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TERATOMA TESTIS

FIFTEEN CASES STUDIED MICROSCOPICALLY AND BIOLOGICALLY

C. W. STELLE, M.D.
Lieut. (j. g.) M. C., U. S. Navy
BROOKLYN

Ewing,[1] in 1911, after a special study of malignant tumors of the testicle, came to the conclusion that "with relatively few exceptions tumors of the testicle belong in the embryonal class and that the great majority or possibly all of these embryonal tumors are of teratomatous origin." He classified testicular teratomas as follows: (1) adult embryomas or teratomas; (2) embryoid, teratoid or mixed tumors; (3) embryonal malignant tumors, and (4) miscellaneous tumors. He stated that the most common malignant tumor of the testis is embryonal carcinoma, alveolar or diffuse, with polyhedral or round cells and often with lymphoid stroma, which is probably a one-sided development of teratoma.

This view was contrary to the belief of Chevassu,[2] who in 1906 classified the testicular tumors in the 128 cases which he reported as follows:

	Cases
Seminal epithelioma	59
Interstitial cell tumor	1
Testicular adenoma	3
Fibroma	1
Sarcoma	1
Embryoma	62
Secondary tumor	1
Total	128

He stated that the majority of malignant testicular tumors were either degenerated embryomas or seminomas (a solid tumor arising from the epithelium of the seminiferous tubules). He held that the latter were not teratoid in origin and stated that he could not find any relation between the two groups, in which 121 of his 128 tumors were included.

Ewing[1] also stated that the seminal epithelioma, or seminoma, of Chevassu is not distinct from the malignant embryoma, but that it is an embryoma or teratoid tumor in which there is a one-sided cellular development resulting in a tumor made up of homologous cells with lymphoid stroma.

From the Cancer Service of the United States Naval Hospital.

1. Ewing, J.: Teratoma of the Testis and Its Derivatives, Surg., Gynec. & Obst. **12**:230, 1911.

2. Chevassu: Tumeurs du testicle, Thèse de Paris, no. 193, 1906.

That the views expressed by Ewing are correct is practically proved by the fact that in all cases of teratoma testis and of so-called seminoma of Chevassu, prolan A (the follicle-ripening hormone of the anterior pituitary body) can be detected in the urine by biologic means.

Ferguson and his associates [3] recently showed that in all patients with teratoma testis examined by them in whom either the primary growth or any metastases remained active, the Aschheim-Zondek test was positive. In the series of cases reported here the same results were obtained.

It must be admitted, then, that embryonal carcinoma or teratoma is by far the most common of the malignant tumors of the testis. Since June, 1930, fifteen patients with malignant testicular tumors have been admitted to the United States Naval Hospital. All of the growths were teratomas. Stevens and Ewing,[4] in 1928, reported a case in which they classified the growth as an adult teratoma; they concurred with the findings of Bell,[5] who reported four similar cases. This tumor differs from embryonal teratoma in that it usually occurs in men past the age of 40, arises from the body of the testis, is far less malignant and metastasizes much later.

ETIOLOGY

The etiology of teratoma testis, like that of all malignant neoplasms, remains unsolved. That trauma plays a part cannot be denied. Dean,[6] who reported 124 cases, found that in only 11 per cent could the onset of symptoms be attributed to an injury. Coley,[7] however, stated that trauma was an exciting factor in 33 per cent of his cases. In the present series 2 of the 15 patients, or 13.3 per cent, said that injury was apparently the cause of the first swelling noticed.

Teratoma is said to occur more frequently in undescended than in normally descended testicles. Dean,[8] quoting Howard, who examined many thousands of men in London hospitals, reported that 0.06 per cent of men have undescended testicle. Dean also stated that teratoma occurs 237 times more frequently in undescended than in normally descended testicles. In the normally placed testis, teratoma usually occurs between

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3. Ferguson, R. S.; Downes, H. R.; Ellis, Edward, and Nicholson, M. E.: Preliminary Note on a New Method of Differentiating the Testicular Tumors by Biological Means, Am. J. Cancer **15**:835 (April) 1931.

4. Stevens, A. R., and Ewing, J.: Adenocarcinoma of the Testis in the Adult, Ann. Surg. **87**:1074, 1928.

5. Bell, G.: Adult Teratoma, Brit. J. Surg. **13**:282, 1925.

6. Dean, A. L., Jr.: Epithelioma of Penis and Teratoid Tumors of Testis, Am. J. Surg. **5**:32 (July) 1928.

7. Coley, W. B.: Cancer of the Testis, Tr. South. Surg. & Gynec. A. **27**:17, 1914.

8. Dean, A. L., Jr.: Early Symptoms and Diagnosis of Carcinoma of the Genito-Urinary Organs, Am. J. Surg. **8**:988, 1930.

the ages of 30 and 40. The average age in the present series was 36.2 years. This is the period of man's greatest motor and sexual activity. In a case in this series (case 2) the patient had an undescended testicle, but the teratoma occurred in the testis on the opposite side.

Ewing [1] came to the conclusion that teratoma testis arises from sex cells in the neighborhood of the rete; the normal development of these cells into spermatogonia has been suppressed, but their potencies remain intact and ready to express themselves in various forms of simple or complex teratoma. He based his conclusions on the fact that teratoma shows a predilection for sex organs and for the development of abortive fetal membranes.

INCIDENCE

Simons [9] stated that teratoma testis is rare; among 300,000 patients admitted to the Mayo Clinic there were only 50 with malignant disease of the testicle. At the United States Naval Hospital, from June, 1930, to Nov. 1, 1932, in 14,381 admissions there were 15 proved cases, or an incidence of 0.001 per cent. During this period there were approximately 620 cases of all types of cancer, in 0.024 per cent of which the growths were teratomas. (No other type of malignant testicular tumor was seen.)

DIAGNOSIS

The diagnosis of malignant testicular tumor, which in the past has created much discussion, is now comparatively simple, owing to a more accurate interpretation of the microscopic observations, careful physical examination and the use of the Aschheim-Zondek test to detect the presence of prolan A in the urine. The most common complaint is a gradual painless enlargement of the testicle or scrotum. These patients are usually under 40 years of age. In about 13.3 per cent of cases, the patient thinks that he first noted the swelling following trauma. The rest of the patients do not connect the enlargement with trauma, either gross or trivial. However, when there is a small painless growth, the patient's complaint may be pains in the back, a lump in the abdomen, a pulmonary disorder or enlarged glands in the neck above the clavicle.

Inspection.—One usually sees a unilateral enlargement of the scrotum, without signs of inflammation unless the tumor is of relatively long standing and has fungated through the skin. Dean [6] recently pointed out that in teratoma there is no apparent retraction or shortening of the penis, such as is seen so frequently in hydrocele. Teratoma cannot be visualized by transillumination unless some portion shows cystic degeneration.

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9. Simons, Irving: The Pathology and Treatment of Malignant Neoplasms of the Testicle, Am. J. Surg. **15**:261 (Feb.) 1932.

Palpation.—Careful palpation of the ordinary teratoma reveals that only the testis is involved. The normal shape of this organ is usually maintained, owing to the density of the tunica albuginea. The epididymis is rarely involved. The teratoma is firm; it may even be stony hard. Pain is not elicited, as a rule, even if the testicle is squeezed. Often the epididymis cannot be palpated when the tumor has reached a great size.

Careful attention should be given to the examination of the rest of the body, particularly of the abdomen, the chest and the supraclavicular fossae. Often the only pathologic condition demonstrable is a palpable mass in the abdomen or enlarged supraclavicular lymph nodes. These signs are frequently present when the original tumor has begun to metastasize. Rectal examination should never be omitted. In addition to the search for metastases, the breasts should be closely examined. Gynecomastia occurs occasionally and is evidenced by a diffuse enlargement, usually on both sides. The breasts are slightly tender, and at times colostrum can be expressed. This phenomenon occurred in a case in the series reported.

Differential Diagnosis.—The differential diagnosis of testicular neoplasms is not without pitfalls, but even when the examiner is inexperienced a correct diagnosis can be made in practically every case if he obeys a few simple rules and makes a careful examination of the tumor. Hydrocele, gumma, tuberculosis and epididymitis are frequently confused with teratoma. I saw a case in which orchidectomy was done for a supposed hydrocele and the patient was later admitted to the Naval Hospital with large metastatic abdominal tumors, although he had been told that he was cured. Hydrocele can usually be transilluminated, the testis can be palpated and, as was pointed out, there is often retraction or apparent shortening of the penis. The fluid contents may be removed by aspiration, but this is not usually necessary.

In gumma the Wassermann test of the blood or that of the spinal fluid or both are positive, and as a rule other signs of syphilis can be found. A provocative Kahn test may also be made. A therapeutic test with intravenous injections of neoarsphenamine in cases of gumma causes marked regression of the tumor, but much valuable time is lost since the results cannot be ascertained for two or three weeks.

Tuberculosis usually occurs in the epididymis, and the characteristic swollen, tender epididymis with nodules extending up the vas is usually sufficient to rule out teratoma, which does not show signs of inflammation unless it is of long duration and is beginning to ulcerate and fungate.

Epididymitis is accompanied by urethritis, either specific or nonspecific, and there is extreme tenderness. The temperature usually is elevated, and rectal examination reveals a tender prostate in many cases.

Orchitis may occasionally require differentiation, but in this condition a history of recent trauma and a painful, inflamed and swollen testis rule out teratoma.

Aschheim-Zondek Test of Urine.—Of prime importance in the diagnosis of testicular neoplasms is the search for prolan A in the urine. This test should never be overlooked, as it now forms the basis of diagnosis. It is particularly valuable because if it is made prior to orchidectomy, in the case of a teratoma, prolan A can practically always be detected in the urine by biologic means. This test, as is well known, utilizes the genitals of immature female mice. A fresh morning specimen of urine is injected into the subcutaneous tissues of the mice. When the test is positive, well defined reactions occur in the ovaries and genital canal within a hundred hours. These reactions consist of ripening of the follicles, hyperemia of the ovary, hemorrhage into the follicles and at times formation of corpus luteum atresia.

Besides being a definite aid in the diagnosis of malignant testicular tumors, the Aschheim-Zondek test of the urine is also valuable in the detection of recurrences and metastases, for, as was pointed out, when either the original tumor or metastasis is present, prolan A can be detected by biologic means. Teratomas are radiosensitive, and when they are treated with well directed, sufficiently strong radiation, the size of the tumor, and particularly the metastases, usually regress sharply; and with this regression the number of mouse units per liter of urine also decreases. The urine should be examined at frequent intervals, and it is important to make both qualitative and quantitative tests. Many weak reactions may be passed over on gross examination, so it is valuable to make sections of the ovaries and study them microscopically (Ferguson [3]).

Microscopic Features.—The following forms may be distinguished microscopically:

1. Embryonal carcinoma with lymphoid stroma. This tumor is usually composed of large, round or polyhedral, embryonal cells, lying diffusely or in large alveoli. The stroma is plentiful and often infiltrated with lymphocytes.

2. Solid embryonal carcinoma. Occasionally the cells are very closely packed together, with scanty stroma (fig. 1).

3. Embryonal adenocarcinoma. When the cells assume an adenomatous structure this term is used. The stroma may be lacking or may be present in large amounts infiltrated with lymphocytes.

4. Chorionepithelioma. Ewing [10] stated that the structure of the testicular chorioma is an exact duplicate of that of the uterine chorioma,

10. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 842.

which presents an overgrowth of all elements of the chorionic villi, connective tissue core, Langhans' cells and syncytium. The type usually seen is the adenocarcinoma. None of the tumors reported here were of this type, which is the rarest malignant testicular tumor.

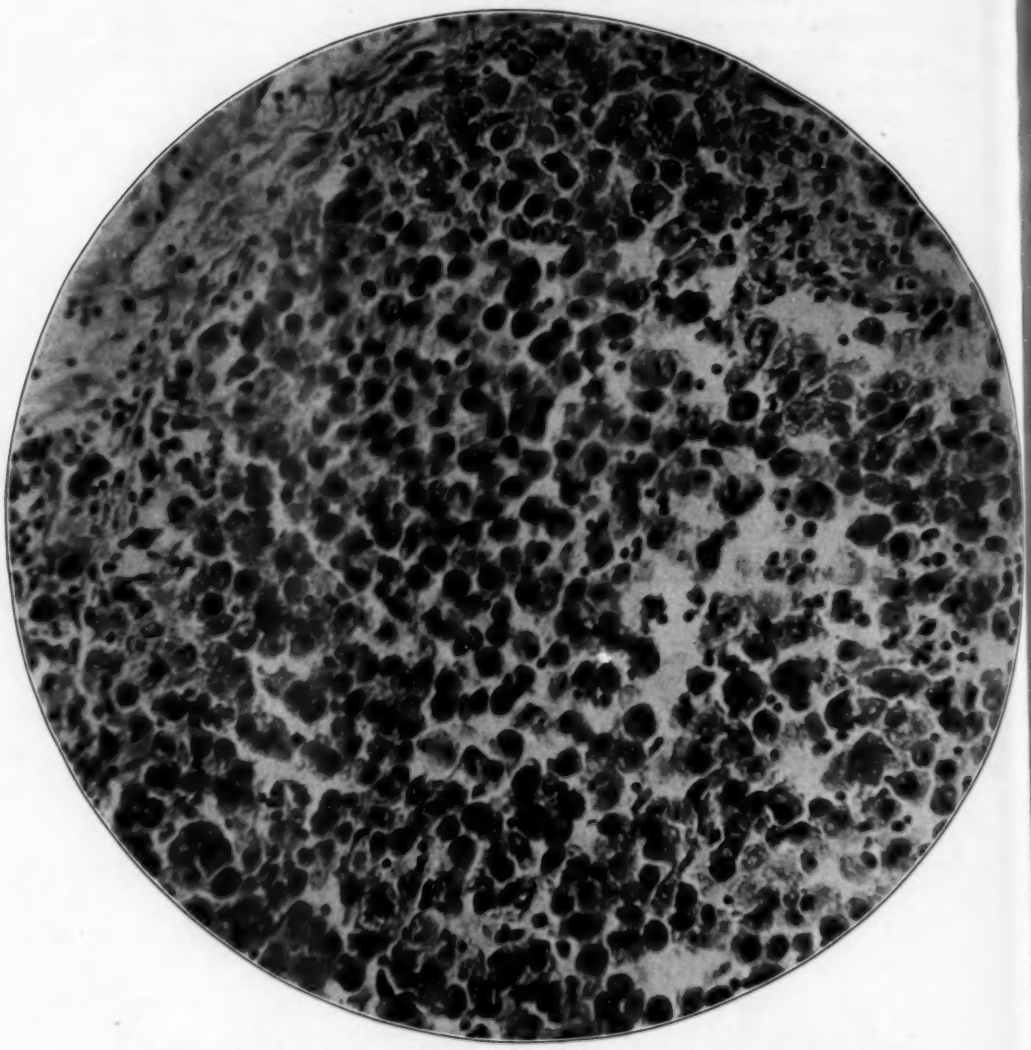

Fig. 1 (case 9).—A section from a solid embryonal carcinoma with scanty lymphoid stroma.

In the 15 cases reported, 11 growths were classified as embryonal carcinoma with lymphoid stroma, 2 as embryonal adenocarcinoma and 1 as solid embryonal carcinoma. The remaining tumor (case 1) which was heavily irradiated prior to orchidectomy, showed at operation only

fibrosis due to the radiation. The test of the urine, however, was positive before the institution of radiation therapy.

Roentgenologic and Metastatic Features.—Embryonal carcinoma metastasizes early by both the lymphatics and the blood stream. The lymphatic metastases are usually to the prevertebral, mediastinal and supraclavicular lymph nodes. Metastasis by way of the blood stream is evidenced by the fairly characteristic roentgenogram of the chest which reveals numerous rounded areas of varying sizes and of increased density, indicating the deposition of tumor cells in small veins from which growth occurs usually in *all* directions (fig. 2).

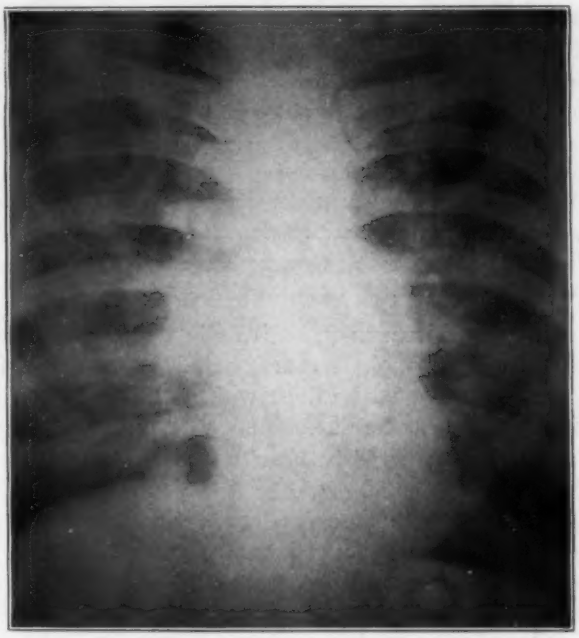

Fig. 2 (case 14).—Roentgenogram of the chest showing multiple exudative nodules throughout both pulmonary fields typical of metastases from teratoma testis.

TREATMENT

Once the diagnosis is established, a definite course of treatment must be decided on. Because patients on admission to the hospital present different stages of the disease, the tumors should be classified as follows, according to Dean [6]:

Group 1. Primary operable: testicular tumor with no evidence of metastases.

Group 2. Primary inoperable: testicular tumor with evidence of metastases.

Group 3. Recurrent operable: operation elsewhere; local recurrence with no evidence of metastases.

Group 4. Recurrent inoperable: operation elsewhere; local recurrence plus metastases.

Group 5. For postoperative prophylactic radiation: operation elsewhere; no evidence of recurrence or metastases.

Barringer [11] stated "that in no tumor has radiation produced more brilliant results than in teratoma of the testis." Surgical treatment, therefore, should be considered secondarily. In a case in which the tumor belongs to group 1, the following procedure should be pursued:

1. The taking of a complete history and physical examination, as well as roentgen examination of the chest.
2. An Aschheim-Zondek test of the urine (particularly quantitative).
3. A preoperative cycle of irradiation, applied as follows:
   A. To the perineum and groin anteriorly, 850 roentgens.
   B. To the abdomen anteriorly and posteriorly, 850 roentgens.
   C. To the lower portion of the abdomen, 850 roentgens.
   D. To the middle portion of the abdomen, 850 roentgens.
   E. To the epigastrium, 850 roentgens.
4. Orchidectomy from six to ten weeks after the last roentgen treatment.
5. An Aschheim-Zondek test a week following operation.
6. Examination of the patient at frequent intervals for evidence of recurrence and metastasis and examination of fresh morning specimens of urine.

When treated in this manner, patients in whom the tumor has not invaded the blood or lymph streams should be assured of complete recovery. Castration should be done with as little trauma as possible in order to eliminate possible dissemination of tumor cells.

Tumors in group 2 should be heavily irradiated, and the output of hormone should be eliminated or reduced to very small amounts before castration is attempted. The operative removal of metastases from malignant testicular tumors should never be attempted.

In group 3, the local recurrent growth in the scrotum may be removed surgically provided there are no metastases, but only after a cycle of radiation therapy.

Tumors in group 4 are usually far advanced and should be heavily irradiated in order to give the patient as much relief as possible. The prognosis is unfavorable.

In group 5, the prognosis is usually good, but a prophylactic cycle of roentgen treatment should be given and the urine examined at frequent intervals in order that possible metastases may be detected at the earliest possible date.

It is too soon for definite conclusions as to the results of treatment to be drawn. Teratoma testis is a very malignant tumor, and the mor-

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11. Barringer, B. S.: Radium Therapy of Tumors of the Genito-Urinary Tract, Am. J. Surg. **7**:243, 1931.

Data on Fifteen Cases of Teratoma Testis

Case	Name	Age, Years	First Symptoms	Physical Findings on Admission to Hospital	Aschheim-Zondek Reaction	Microscopic Diagnosis	Treatment
1	P. C.	33	Painless enlargement of testis	Large firm painless mass filling entire left side of scrotum; no evidence of metastasis	Positive	Radiation fibrosis; no remaining evidence of cancer	External radiation and orchidectomy
2	A. D.	31	Painful enlargement of left testis	Left testis firm and tender, right testis congenitally absent; no metastasis	Positive	Embryonal adenocarcinoma	External radiation and orchidectomy
3	H. D.	42	Gradual painless enlargement of left testis	Left testis absent; no evidence of metastasis	Negative	Embryonal carcinoma	External radiation
4	H. N.	35	Gradual painless swelling of right testis	Right orchidectomy; metastasis to abdomen, scalp, lymph nodes and lungs	Positive	Embryonal carcinoma	External radiation
5	J. Mc.	35	Painful swelling of left testis	Enlarged, slightly painful, firm left testis; no metastasis	Positive	Embryonal carcinoma with lymphoid stroma	External radiation and orchidectomy
6	D. M.	41	Hard painless enlargement of left testis	Left orchidectomy; metastasis to abdomen	Positive	Embryonal carcinoma with lymphoid stroma	External radiation
7	N. D.	30	Gradual painful enlargement in scrotum	Left orchidectomy; recurrence in scrotum; metastasis to lung and abdomen	Positive	Embryonal carcinoma with lymphoid stroma	External radiation
8	H. S.	36	Gradual firm painless swelling of left testis	Enlarged firm painless left testis; no evidence of metastasis	Positive	Embryonal carcinoma with lymphoid stroma	External radiation and orchidectomy
9	R. B.	32	Gradual slightly painful enlargement of left testis	Left orchidectomy; no evidence of metastasis	Negative	Solid embryonal carcinoma	External radiation
10	A. B.	36	Gradual painless enlargment of right testis	Right orchidectomy; metastasis to abdomen	Positive	Embryonal carcinoma with lymphoid stroma	External radiation
11	M. D.	41	Gradual slightly painful enlargement of right testis	Right orchidectomy; metastasis to abdomen	Test not made; patient said to have had tuberculosis	Embryonal carcinoma with lymphoid stroma	Patient died before treatment could be instituted
12	T. M.	38	Gradual painless enlargement of left testis	Left orchidectomy; no evidence of metastasis	Negative	Embryonal carcinoma with lymphoid stroma	External radiation
13	E. J.	44	Slightly painful enlargement of left testis	Left testis enlarged and painful	Positive	Embryonal carcinoma with lymphoid stroma	External radiation and orchidectomy
14	R. W.	33	Gradual painless enlargement of right testis	Enlarged right testis; metastasis to lymph nodes, chest and abdomen; gynecomastia	Positive	Embryonal adenocarcinoma and diffuse carcinoma	External radiation and orchidectomy
15	T. H.	36	Painless enlargement of left testis	Left orchidectomy; metastasis to abdomen	Positive	Embryonal carcinoma with lymphoid stroma	External radiation

tality is exceedingly high. In several cases in which the diagnosis was made early and the tumor was irradiated both before and after operation, the patients are alive and well, apparently free from disease. I intend to report the mortality rates at a later date.

It will be seen that in the accompanying table only a brief line is given to the treatment in each case. I wish in this paper to stress particularly diagnosis, early treatment and the use of the Aschheim-Zondek test.

Occasionally the growth in the testis may be so small as to escape detection in the preliminary examination. Metastasis may have already taken place, and the patient may consequently complain of a mass in the abdomen or of enlarged glands in the neck. Recently a patient was admitted to the hospital with a diagnosis of benign tumor of the abdomen. At exploratory laparotomy an inoperable retroperitoneal tumor was found. Biopsy showed embryonal adenocarcinoma, and prolan A was detected in the urine. Examination showed that the testicles were apparently not involved. Autopsy was not permitted, and therefore the testicles were not examined microscopically. Ewing [12] emphasized "the necessity of careful palpation of the testis in male subjects presenting tumors of any sort in the abdomen or chest." In doubtful cases, application of the Aschheim-Zondek test will prove or disprove the malignant teratomatous nature of the growth.

CONCLUSIONS AND SUMMARY

1. After a study of 15 cases of malignant tumor of the testicle and a brief review of the literature on the subject, I am of the opinion that practically all malignant testicular growths are either embryonal carcinomas or embryonal adenocarcinomas of teratomatous origin. No other type of malignant disease of the testicle has been seen at the United States Naval Hospital since June, 1930. That another type does occur has been pointed out by Stevens and Ewing and by Bell, who described an adult teratoma.

2. Fifteen cases are included in the accompanying table. In all the cases in which either the original tumor or active metastases were present prolan A could be detected in the urine biologically, by means of the method of Aschheim and Zondek.

3. A short résumé of the diagnosis, differential diagnosis and treatment of teratoma testis is given.

4. The importance of making a quantitative test for prolan A in all cases that show a negative qualitative reaction is stressed.

5. Teratoma testis is comparatively rare, only 15 cases having occurred in 14,381 general admissions to the hospital in a period of

12. Ewing, J.: Extra-Testicular Teratoma of the Testis, Proc. New York Path. Soc. **13**:26, 1913.

twenty-eight months. During this same period, there were approximately 620 cases of cancer, in 0.024 per cent of which the growth was a teratoma.

6. Teratoma testis is relatively radiosensitive, and treatment by external radiation and by surgical intervention produces results varying from complete cures to palliative effects assuring the patient months or even years of life comparatively free from disease.

7. It is believed that unless the surgeon has all the requisite facilities at hand, such as equipment for roentgen therapy and a laboratory for the making of the Aschheim-Zondek tests, he cannot give patients with these tumors the full benefit of present day treatment. It is better to turn them over to an institution that is well equipped than merely to excise the tumor, hoping that one has cured the patient, and then have him return a few months later hopelessly ill with metastases to the retroperitoneal lymph nodes and to the lungs.

EXPERIMENTAL LUMBAR SYMPATHECTOMY

I. EFFECTS ON VASCULAR TREE, REACTIVE HYPEREMIA AND TEMPERATURE OF SKIN OF EXTREMITIES

PAUL E. McMASTER, M.D.
AND
NORMAN W. ROOME, M.D.
CHICAGO

The effects of lumbar sympathectomy on the lower extremities have been extensively studied, but the results in certain respects have been sufficiently conflicting to warrant further investigation.

In this paper will be included roentgenologic observations on the peripheral vascular tree, studies on reactive hyperemia and observations on the temperature of the skin.

In all the experimental work to be presented, unilateral lumbar sympathectomy was performed, usually on the left side. This included excision of four ganglions and the intervening chains from the sacral promontory upward. Healthy adult dogs were used, and the operations were performed under morphine-ether anesthesia, aseptic technic being used.

EFFECT ON THE PERIPHERAL VASCULAR TREE

Horton and Craig [1] did unilateral lumbar sympathectomies on dogs. Two to three weeks after sympathectomy, they injected metallic mercury into the aorta, after bleeding the animal, and then made roentgenologic studies of the hindlimbs. They stated that the vascular tree of the hindleg on the side on which the operation had been performed was definitely dilatated when compared to the normal condition of the opposite leg.

Similar studies were made by us. Eleven dogs were studied at intervals of from six to one hundred and eleven days after sympathectomy. Each dog was bled from the carotid artery. The abdominal aorta was cannulated and the radio-opaque material to be injected was fed, being introduced by means of gravity. The material used was a preparation of vermilion water color, which has a mercury base and is a thick paste; it is ordinarily used for lettering show cards and for

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From the Department of Surgery, the University of Chicago.

1. Horton, B. T., and Craig, W. M.: Evidence Shown in Roentgenograms of Changes in the Vascular Tree Following Experimental Sympathetic Ganglionectomy, Arch. Surg. **21**:698 (Oct.) 1930.

painting purposes. This was mixed with water until a thin suspension resulted, and was then injected.

Into some of the animals this solution was injected while they were being bled; into others, immediately after the bleeding. In four of the dogs, the inferior vena cava was cannulated, and through the aortic cannula the vascular system to the hindlegs was first perfused with a physiologic solution of sodium chloride. The material to be injected was then introduced.

Roentgenograms were first taken immediately after the opaque solution was injected, when the pressure was very low. Subsequent pictures were taken as the pressure of the solution was increased, until

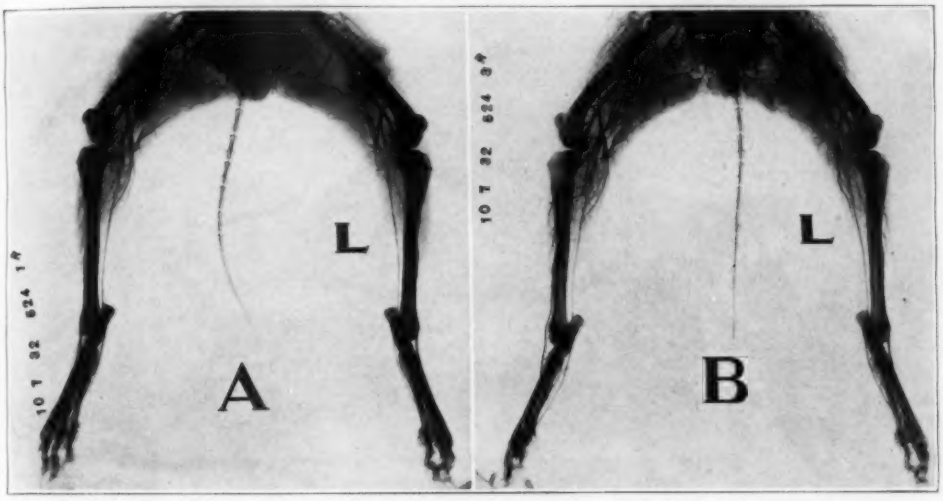

Fig. 1.—Injections into the vascular tree fifteen days after lumbar sympathectomy on the left side. *A* was taken immediately after the material was introduced; *B* was taken after the material was introduced under pressure. In *A* more vessels about the right knee show the material injected than on the left, sympathectomized side (*L*).

the vascular trees were well filled. In none of the pictures taken was there any increased filling in the vessels of the side on which the operation had been performed (fig. 1). On dissection, it was found that the injected material had not reached the veins.

Since the veins were devoid of the material injected, this had not passed through the capillaries. Thus the larger arterioles were probably the smallest branches into which the material had passed that were shown in the roentgenograms. This would suggest that the vascular changes following experimental lumbar sympathectomy in dogs probably take place in the smaller arterioles and capillaries.

EFFECT ON REACTIVE HYPEREMIA

Reactive hyperemia has been studied by Goldblatt [2] and found to occur in limbs denervated by division of peripheral nerves and to be similar to that observed in normal extremities. There is no record of observations on reactive hyperemia following lumbar sympathectomy.

The present studies were made as follows: At various intervals following the lumbar sympathectomy, a plethysmograph was placed on the hindlimb of the side on which the operation had been performed and the volume of the limb was recorded on a smoked drum. The femoral artery was isolated. Normal tracings were then made, after which the femoral artery was temporarily clamped for periods varying from a second to a minute. Four experiments were performed seven, fourteen, one hundred and three and one hundred and thirteen days following sympathectomy. In all cases, the hyperemia was found to

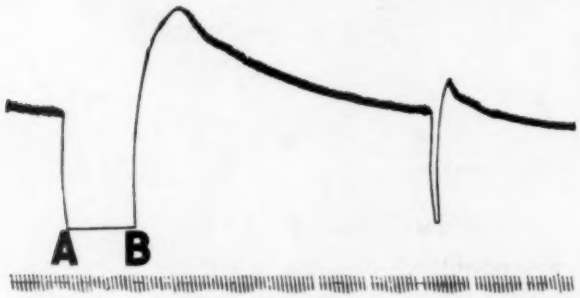

Fig. 2.—Kymograph tracing of volume of limb, illustrating reactive hyperemia in sympathectomized limb; time markings, five seconds and minutes. *A* indicates obstruction of artery; *B*, release.

be the same as for the limbs in which sympathectomy had not been performed. Figure 2 shows a portion of a typical tracing.

CHANGES IN TEMPERATURE

Craig and his co-workers [3] noted that following a general anesthetic there is a sharp rise in the surface temperature of all four extremities. These authors and also Baldes and his co-workers [4] have shown that the

2. Goldblatt, Harry: Reactive Hyperaemia, Heart **12**:281, 1926.

3. Craig, W. M.; Horton, B. T., and Sheard, Charles: Thermal Changes in Peripheral Vascular Disease During Sympathetic Ganglionectomy Under General Anaesthesia, Proc. Staff Meet., Mayo Clin. **7**:537, 1932.

4. Baldes, E. J.; Herrick, Julia F., and Essex, H. E.: The Measurement of Flow of Blood and the Effects of Anesthesia and Lumbar Sympathectomy, Proc. Staff Meet., Mayo Clin. **7**:535, 1932.

vasodilatation in the extremities accompanying a general anesthetic is maximal and cannot be increased by sectioning the sympathetic chain.

Studies of temperature were made by us with the use of a thermocouple. No definite or constant changes in the temperature of the skin were found in the feet or legs immediately after sympathectomy. However, after the effects of the anesthetic had disappeared, a higher temperature was found on the sympathectomized side. Since our findings correspond with those of previous observers, the results are given only in summary. The most marked increases were present in the paw of the side on which the operation had been performed. Higher readings were also found over the calf on this side as compared to those of the control. On the more proximal portions of the thigh, the differences in readings on the two sides were slight, and in a number of cases the temperatures were equal.

The increases in temperature in the paws ranged from 0.5 C. to nearly 2 C. on the sympathectomized side. One dog showed a reading higher by 0.8 C. in the paw on the side on which the operation had been performed five months after sympathectomy. Equalization of the differences in the skin temperature of the two sides usually took place from three to four months following sympathectomy. No differences in temperature were found in four dogs five months after the operation.

SUMMARY AND CONCLUSIONS

1. There was no dilatation of the peripheral vascular tree demonstrable roentgenologically after injection of an opaque solution following unilateral lumbar sympathectomy, when compared to the opposite side.

2. The period of reactive hyperemia in the extremity was not altered from the normal by unilateral lumbar sympathectomy.

3. There was no constant increase in peripheral temperature in the hindleg immediately after unilateral lumbar sympathectomy, while the animal was still under the influence of ether anesthesia. Increased temperature readings were obtained in the leg on the sympathectomized side after the anesthetic effects wore off, and persisted for approximately three to five months. These were most marked in the peripheral portions of the limb.

TUMORS OF THE SYMPATHETIC NERVOUS SYSTEM

NEUROBLASTOMA, PARAGANGLIOMA, GANGLIONEUROMA

DEAN LEWIS, M.D.
AND
CHARLES F. GESCHICKTER, M.D.
BALTIMORE

Many reports of tumors arising within the sympathetic nervous system have appeared during the past few years. Many of the tumors were described early. Virchow, in 1864, described an undoubted tumor of the sympathetic system, designating it a glioma. Wright, in 1910, gave one of the best descriptions of one variety of these tumors, such a one as was described by Virchow, and placed these on a sound pathologic basis. The paragangliomas or chromaffin tumors were first described by Manasse in the suprarenal gland in 1893. Frankel (1886) and Perley (1890) apparently described tumors of this type. The third type, ganglioneuromas, were first described by Loretz in 1870. The literature on these tumors has been reviewed several times during recent years. The number of cases studied by any one person has been relatively small. There are one hundred and three case records of these tumors in the Johns Hopkins Hospital in which the clinical and pathologic findings are recorded.

NEUROBLASTOMAS

These tumors have the same embryologic origin as the medulla of the suprarenal gland and the adjacent sympathetic ganglions; they arise from the neuroblasts (sympathogonia), which wander out from the neural crest to form the structures in the sympathetic system. The similar histologic appearance of the neuroblast and the cells of the neuroblastoma indicates the relation between the two. Different degrees of differentiation account for the occurrence of various types of tissue in the same tumor. A paraganglioma may have scattered through it islands resembling the tissue of a neuroblastoma. The small cells with heavily staining nuclei and poorly defined cytoplasm that predominate in the neuroblastoma develop from cells which migrate outward to form the sympathetic ganglions and chromaffin tissue. The position these assume and the ages at which they are found correspond with the site

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From the Harriet Lane Home and the Surgical Pathological Laboratory of the Johns Hopkins Medical School and Hospital

at which these tumors appear and the age at which they develop. These tumors develop where the cells normally persist. The tumor probably does not develop from misplaced rests.

We have studied forty neuroblastomas. Thirty-three were in the medulla of the suprarenal gland or in the sympathetic ganglions adjacent to the medulla. Slightly less than one half of these tumors developed

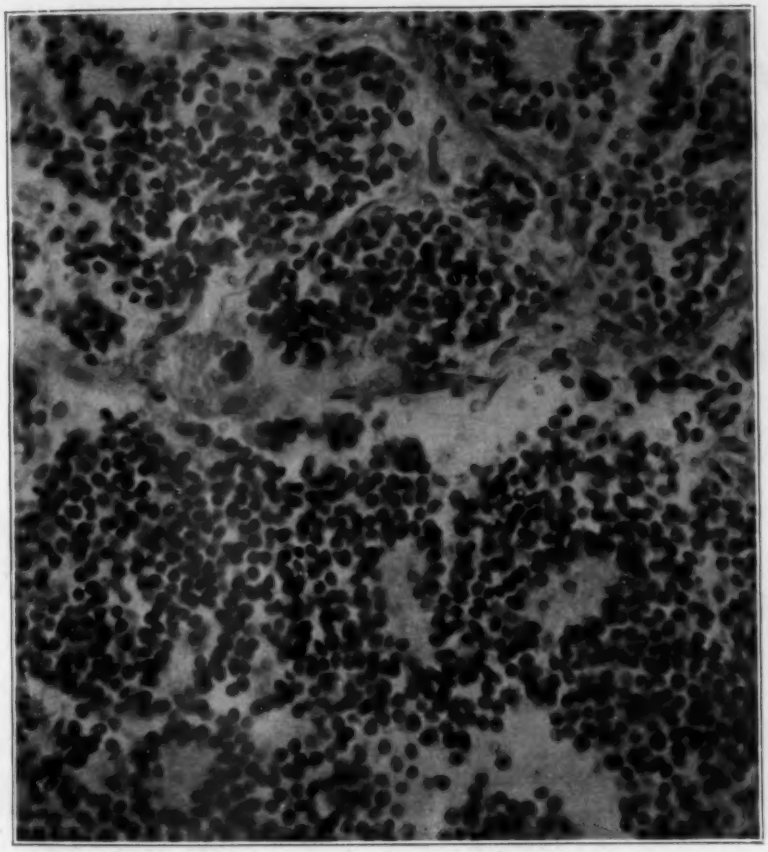

Fig. 1 (path. no. 2216).—Typical neuroblastoma of the suprarenal gland with rosettes occurring in an infant of 18 months and metastasizing to the liver and lung. This illustration emphasizes the extremely small size of the cells, the deeply staining nuclei and the tendency of the cells to arrange themselves about a small central area (rosette formation).

in children under 3 years of age. Only five of the patients were over 15 years of age. Reid found that over 80 per cent of neuroblastomas occurred in patients under 2½ years of age. Wright and Landau each reported cases in stillborn infants. In one of our cases a neuroblastoma

in the suprarenal gland had metastasized to the liver of an unborn child. The enlarged liver prevented delivery, and the fetus was sacrificed and the liver morcellated in order to permit of birth.

The most common symptoms are fever, abdominal mass and anemia. The tumor may cause pressure on the abdominal viscera, giving rise to vomiting. Frew, in 1911, described a case of neuroblastoma in which the symptoms noted resembled those of acute rheumatic fever. In two of the patients observed by us, aged 3 and 4½ years, respectively, the

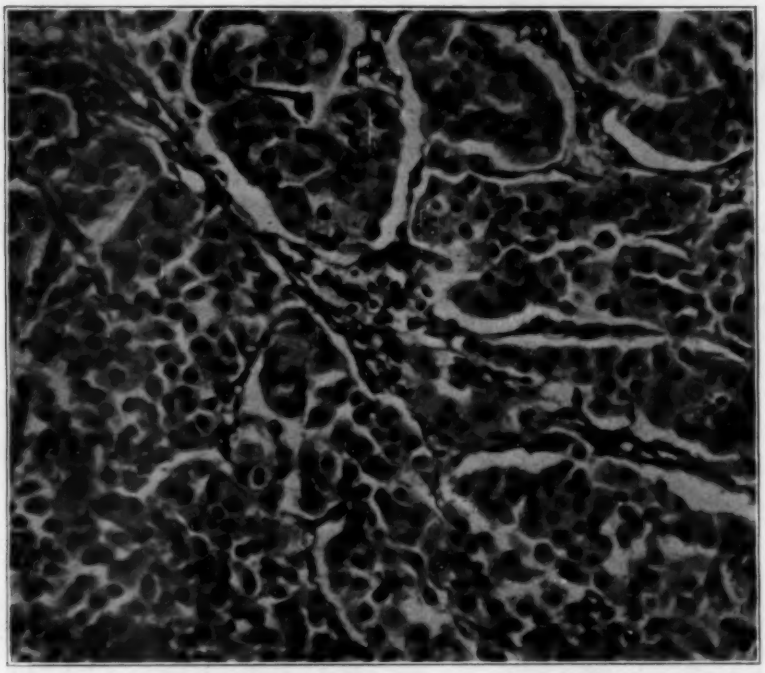

Fig. 2 (path. no. 46958).—Benign paraganglioma of the medulla of the suprarenal gland occurring in a white woman, aged 53, and producing symptoms referable to the kidney. The patient has remained well following excision. The photomicrograph shows cells of moderate size containing a distinct amount of cytoplasm with an alveolar arrangement. Along the strands of tissues forming the stroma of the tumor are seen aggregations of extremely small cells of the neuroblastoma type.

disease at the onset resembled acute rheumatic fever, with high temperature and involvement of many joints. In some instances there is a marked anemia with a low platelet count.

In five of our cases an exploratory laparotomy was performed. A mass could be palpated; muscular tenderness and rigidity were noted, and the disease had progressed rapidly. The clinical picture of appendicitis was simulated.

The following histories will be given to illustrate how protean the clinical picture may be:

Neuroblastoma of the Medulla of the Suprarenal Gland in a Stillborn Infant.—A full term fetus could not be delivered because of obstruction to the pelvic outlet by a large abdominal mass. The abdomen was opened and the liver morcellated to permit of delivery.

An examination revealed that the abdomen was filled with a liver weighing 700 Gm. and measuring 14 by 12 by 6 cm. On the surface of the liver were many

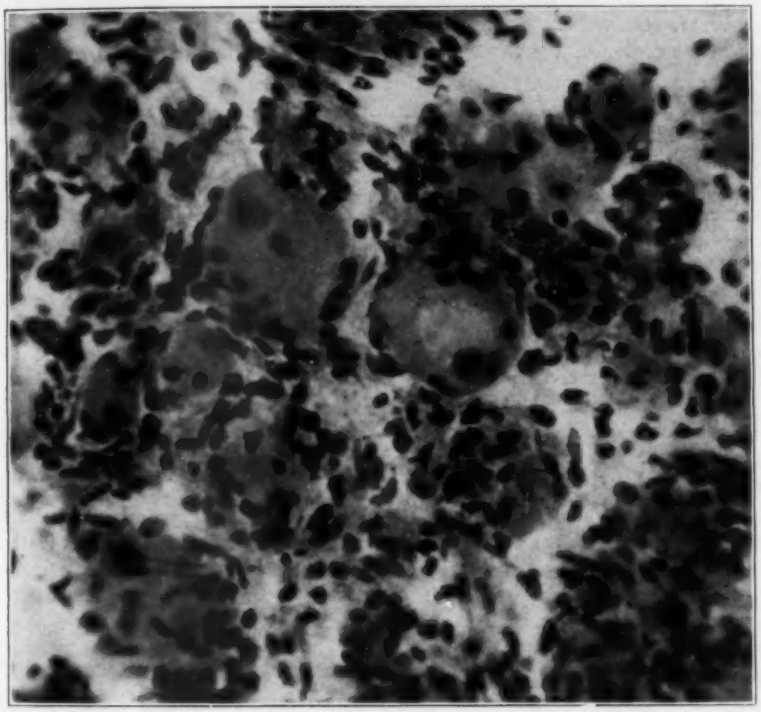

Fig. 3 (path. no. 21763).—Ganglioneuroma of the cervical sympathetic occurring in a white man, aged 41. The tumor had been present for eighteen years and ultimately underwent malignant change. The large ganglion cells with distinct nuclei are separated by a pale staining stroma containing numerous small spindle cells (case previously reported by Lewis and Hart).

irregular white nodules. The cut surface gave the appearance of granite. The right suprarenal was replaced by a mass measuring 6 by 6 by 5 cm., which was attached to the upper pole of the right kidney by a short, fibrous pedicle. This tumor was solid, dark red and encapsulated. On section it appeared like a homogeneous blood clot.

Microscopically, the tumor was quite characteristic of neuroblastoma. Many nests of small round cells were separated by a network of fibrillar stroma. Many of the cell masses had a characteristic rosette arrangement. The cells,

though small, had a delicate, refractile rim of cytoplasm, and the nuclei usually stained heavily, but some degenerating vacuolated nuclei were seen. The differentiation between this tumor and lymphosarcoma (with which it is often confused) may be made by the rosettes and characteristic stroma. By special staining methods definite fibrils could be demonstrated.

Neuroblastoma of the Right Suprarenal Gland; Unilateral Hypertrophy on the Side of the Tumor.—A girl, aged 4, the sixth child born of normal parents, had been delivered spontaneously at full term. Two weeks before admission to the hospital she had vomited during the morning, but had played and seemed well thereafter during the day. One week before this a tumor had been accidentally discovered. On the day of admission the child complained for the first time of pain in the region of the tumor. Definite loss of weight had been noted.

On examination an asymmetry of the extremities was noted (right leg, 41.5 cm.; right arm, 40 cm.; left leg, 40.75 cm.; left arm, 38.5 cm.). A large mass could be palpated in the left upper quadrant. This mass was nodular. Some parts of it seemed soft, almost fluctuant. It extended from the costal margin to the ilium, and toward the midline. The tumor did not move noticeably on respiration. Apparently it was attached at some point to the liver. There was a general enlargement of lymph nodes. Several could be felt just beneath the abdominal wall. These were apparently in the mesentery.

Roentgen examination of the bones of the extremity gave negative results. The blood count was: red blood cells, 5,150,000; white blood cells, 15,350; hemoglobin, 95 per cent; differential count, polymorphonuclears, 81 per cent; large lymphocytes, 15 per cent; mononuclears, 5 per cent, and other forms, 1 per cent. The urine was normal. The temperature ranged between 100 and 101 F. The child remained in the Harriet Lane service for five days. Then an exploratory laparotomy was performed. This revealed an inoperable tumor in the region of the left kidney. A lymph node was removed for diagnosis.

The tissue examined was grayish and translucent. Many opaque, yellowish areas were found. These were softer than gelatin. Microscopically, the tissue was composed of many small cells with oval nuclei, containing deeply staining granules. The cytoplasm was scanty. In some areas there was a suggestion of clumping. No definite rosette formation was noted.

Hutchinson, after studying ten cases of so-called sarcoma of the suprarenal gland in children associated with metastases to the skull, described a definite clinical syndrome as follows:

In the majority of the cases the first thing noticed was some swelling about the bones of the skull, which in several of them was ascribed to a fall or injury. Following or preceding this proptosis of one or both eyes was observed. In two-thirds of the cases discoloration of the eyelids on one or both sides is reported, and in a few instances this was the first point to attract attention. Anemia is a striking feature in all the cases, the blood changes being those of a profound secondary anemia. Leukocytosis has not been recorded in any case. An abdominal tumor in one or the other loin was felt in only five cases. The progress of the disease in every instance has been rapid and the younger the patient the more rapid it appears. Indications of increased intracranial pressure, such as torpor, intense optic neuritis, and blindness may develop. The postmortem features are also very constant; in all there was found a sarcoma of the suprarenal, usually consisting of small round cells situated on the left side in six and on the right side in four

of these cases. The most extensive metastases were found in the bones of the vault and base of the skull, producing swellings on the head and protrusion of the eyes observed during life. Metastases are also met with in the ribs, sternum and vertebrae, but not apparently (except in case 1) in the long bones, though these may not always have been carefully examined.

Neuroblastoma (Hutchinson Type).—Clinically, the symptoms simulated somewhat those of rheumatic fever. The parents were healthy. This child, a girl,

Fig. 4 (path. no. 51971).—Roentgenogram of metastases to bone occurring in a girl, aged 5 years, with neuroblastoma of the suprarenal gland. The child was in the hospital for three months and died two months after her discharge. During hospitalization rapid extension of the bone involvement and retrobulbar metastases involving both orbits occurred. In the roentgenogram of the pelvis and femurs, the bones are diffusely mottled by areas of bone destruction and reactive new bone.

aged 5, had had repeated attacks of tonsillitis since she was 1 year old. Occasional colds in the head accompanied by a mucopurulent nasal discharge had occurred.

Three months before admission the child had complained of pain in the region of the stomach. The pain was accompanied by nausea, and the child had vomited several times. She had remained in bed for some time because of a slight fever. When the child was admitted to the hospital definite manifestations in the joints

were noted, and pain in the left hip was complained of. The child was restless at night, and had marked loss of appetite. No urinary symptoms were noted. The temperature was 101 F. on admission. The child was pale and weak and could not raise herself to a sitting position. No ocular changes were found on admission. Lymph nodes were palpable in the cervical region, in both axillae and in the groins. The heart and lungs were normal. On the first examination the abdomen was found to be flat, and the liver and spleen could not be felt. Marked spasm of the abdominal muscles was, however, noted. When the left leg was passively moved the child complained of pain in the muscles about the knee and pain about the left hip. No tenderness of the bones could be made out.

The blood count on admission was: red blood cells, 3,920,000; hemoglobin, 62.5 per cent; white blood cells, 8,050; with polymorphonuclears, 61 per cent;

A B

Fig. 5 (H. L. H., path. no. 79043 and 79311).—Photographs of children showing Hutchinson and Pepper syndrome produced by neuroblastoma of the suprarenal gland. *A*, Hutchinson's syndrome, shows proptosis of the eye in a boy, aged 3, whose illness began with slight fever, pain in the extremities and prominence of the eyes. He was thought to have acute rheumatic fever. The wound shown is the result of a radical operation on the sinus. The patient died two months after admission to the hospital, five months after the clinical onset of the disease. *B*, Pepper syndrome, shows the tumor mass on the left outlined by palpation. This mass could not be separated by palpation from the liver and spleen. The pyelogram showed the kidney displaced and rotated by the tumor mass. The patient died six days after operation for removal of the tumor.

small lymphocytes, 27 per cent; monocytes, 4 per cent; myelocytes, 7 per cent and eosinophils, 1 per cent.

The roentgen examination revealed definite changes in the upper end of the shaft of the left femur. There were pain and spasm of the muscles in the left

leg. The lymph nodes could be more distinctly felt. Typhoid, a low grade osteomyelitis and a malignant condition were considered in the differential diagnosis. Subsequent roentgen examinations revealed many areas of rarefaction in the upper ends of the femur and humerus and in the bones of the pelvis and skull.

After the child had been in the hospital a month and a half, the right eye became swollen and puffy. Within two and one-half months the cervical lymph nodes became markedly enlarged. Exophthalmos with chemosis developed, and the liver enlarged, extending two fingerbreadths below the costal margin (figs. 4, 5 and 6).

About three months after admission an examination revealed marked bilateral exophthalmos and complete loss of vision of the left eye. A diagnosis of neuroblastoma of the left suprarenal gland with metastases to the left eye was made.

A biopsy specimen was taken under local anesthesia, the tissue being removed from a small nodule in the skull. The bone was extremely porous, and some of

Fig. 6 (path. no. 51971).—Photograph of the patient shown in figure 4 with typical Hutchinson's syndrome. The enlarged cervical nodes and the exophthalmos are more marked on the left.

the tumor was removed with a curet. This tissue was gelatinous. A diagnosis of a neuroblastoma was made from a frozen section. This diagnosis was confirmed by subsequent studies.

In 1901, Pepper published a paper entitled "Congenital Sarcoma of the Liver," in which he said that "a careful review of the literature upon the subject of primary sarcoma of the suprarenal and of the same in the liver was intensely interesting, because I found five cases of such striking similarity to the one that I have just reported that I have thought it important to abstract them quite fully to show that we have here a special type of congenital malignant disease with its own peculiar symptoms and pathological findings."

Bone Metastases.—The roentgen findings in neuroblastoma are quite typical, small multiple areas of rarefaction predominating. Eight patients in our series had multiple metastases to the bone. Of the long bones, the humerus and femur are most often affected. The roentgenograms in these cases reveal many small, discrete areas of destruction of the bone, with an occasional longitudinal zone of rarefaction. A periosteal reaction in which a delicate layer of bone is laid down parallel to the shaft in the long bones and sclerosis of the

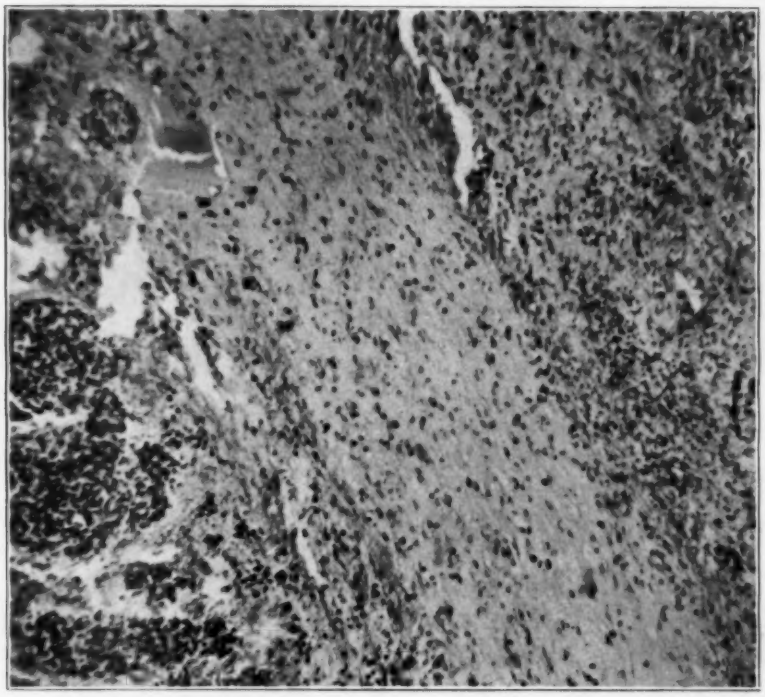

Fig. 7 (gen. path. no. 12854).—Photograph of neuroblastoma of the suprarenal gland occurring in a Negro girl, aged 16 months. The child had a course of five radium treatments and two transfusions followed by excision of the tumor. The operation was followed by pneumonia, otitis media and death. The section shows the necrosis and hyalinization in the tumor produced by the irradiation. Areas of surviving tumor cells are seen in the upper left-hand corner.

marrow cavity are more typical of leukemia or lymphosarcoma of bone. Such changes are rare in neuroblastoma.

Pyelograms are usually negative, but occasionally an obstruction of the ureter and dilatation of the renal pelvis occurs. Metastases to the chest are most frequently found in the mediastinum. In children a flat plate of the abdomen may show a large hazy shadow at the site of

the tumor. This is usually rendered indefinite by the hepatic shadow. The diaphragm on the affected side may be elevated.

The clinical course is progressively downward. The average duration of symptoms in our series before admission to the hospital was six months. One half of the patients had had symptoms for one month or less. In two the tumor was present at birth. When operation was attempted, death occurred within a month. A relatively large proportion of neuroblastomas occurring in children run their course within two months. Although softening and a decrease in the size of the tumor may follow the use of roentgen rays or radium, this treatment seems to hasten the development of metastases. This is difficult to determine, however, when the tumor runs such a rapid course. Surgical intervention seems to affect the course unfavorably. There is one outstanding exception. Lehman reported a case in 1917, in which operation had been performed a year before. The tumor was removed, and the patient was reported well in 1931, fifteen years later.

In both the Hutchinson and Pepper types, metastases may form in the liver and bones before the primary growth attracts attention. Frew attempted to explain these different syndromes. He suggested that in Hutchinson's syndrome the tumor was in the left suprarenal gland and formed metastases by way of the blood stream, while in the Pepper syndrome the tumor developed in the right suprarenal gland and metastasized to the liver by way of the lymphatics. Study of an increasing number of cases has not supported this explanation. The Pepper syndrome is more common in the earlier ages (average age slightly over 1 year), while the tumors giving rise to metastases of the bone and Hutchinson's syndrome occur more frequently at a later age (average over 6 years [Scott and Oliver]).

Pathology.—In three of our cases both suprarenal glands were involved. In five cases recorded in the literature both glands were also involved. In such cases it is difficult to determine whether the tumor was bilateral from the beginning or whether metastases developed in the gland not at first involved. The tumor may be solid or cystic. The growth is usually well encapsulated. The surface is nodular, and the color varies from a light yellow or gray to a dark or hemorrhagic hue. The kidney is frequently compressed. The growth does not usually invade it.

The majority of neuroblastomas are composed of small cells with hyperchromatic nuclei and little cytoplasm. These cells are grouped together in an arrangement which suggests the clumping of staphylococci in culture medium. Rosettes were found in slightly more than one third of our cases. In about one half of the cases collected by Wahl typical rosettes were present. A number of different names (lymphocytoid cells,

TABLE 1.—*Data on Cases of Neuroblastoma at the Harriet Lane Home, Johns Hopkins Hospital*

Path. No.	Sex	Age	Site	Duration	Symptoms	Metastases
Suprarenal Neuroblastomas in Children						
79311 12854	F	16 mos.	Suprarenals	1 mo.	Pallor, loss of weight, abdominal mass, fever	Liver, lymph nodes ?
79043	M	3 yrs.	Suprarenal	3 mos.	Limp, fever, prominence of left eye	Bones, eye, liver ?
67751 47837	F	4 yrs.	Suprarenal	2 wks.	Vomiting, abdominal mass, fever	Lymph nodes, liver ?
55657 51971	F	5 yrs.	Suprarenal	3 mos.	Vomiting, fever, pallor, pain	Bones, lymph nodes, eye
52545 9852	M	9 yrs.	Right suprarenal, left suprarenal	3 wks.	Anorexia, loss of weight, vomiting, mass in abdomen, fever	Kidneys, heart, liver, pancreas, prostate, thyroid, ureter, lymph nodes, bone
47017 9029	M	2 yrs.	Left suprarenal	2 mos.	Anorexia, loss of weight, pain, fever	Left kidney, liver, lymph nodes
42917 8444	F	3 wks.	Left suprarenal, right suprarenal	3 wks.	Drowsy, diarrhea, enlarged abdomen, fever	Liver
42879 8450	M	16 mos.	Left suprarenal, right suprarenal	3 wks.	Cough, pallor, abdominal mass, fever	Liver, lymph nodes, left kidney
39467 41651	M	3 yrs.	Retroperitoneal	5 wks.	Vomiting, mass in abdomen, fever	Kidney, cecum ?
32539 7028	M	23 mos.	Right suprarenal	1 mo.	Pain, vomiting, fever, abdominal mass	Liver, lymph nodes, sigmoid
13366 2216	F	18 mos.	Left suprarenal	1 mo.	Abdominal mass, fever	Liver, left kidney, lung
7647	F	7 mos.	Suprarenal	16 days	Premature infant, acute gastric symptoms	No metastases
4119 4118	M	1 yr.	Right suprarenal	2 wks.	Fever, cough, abdominal mass, pallor, otitis media	Lymph nodes, liver ?
Referred Cases of Suprarenal Neuroblastoma in Children						
46774 Lindsay	M	2 mos.	Left suprarenal	2 mos.	Cough, diarrhea, abdominal mass	Liver
46526 Heise	M	16 yrs.	Right suprarenal	1 wk.+	Right abdominal pain	Kidney, mediastinum, lymph nodes, liver
15307 Kline	M	4½ yrs.	Right suprarenal	2 wks.	Pain in stomach, anorexia, protrusion of right eye	Kidney, liver, lymph node, lung, right orbit
45704 Keasbey	M	4 yrs.	Left suprarenal	1 yr.	Abdominal pain, vomiting	Bones, lymph nodes
49272 C. Smith	M	15 yrs.	Bladder, neck	2 yrs.	Urinary obstruction	Lymph nodes, lung, heart
49528 C. Bruck	M	6 yrs.	Left suprarenal	6 mos.	Abdominal mass, vomiting, pain	Lymph nodes, kidney, bones
46760 E. Smith	Fetus		Right suprarenal	.....	Stillbirth	Liver
49358 Wassing	M	12 yrs.	Coccygeal region	3 mos.	Lump over spine, swelling of genitalia	Lymph nodes, pelvis
43518 Boulware	M	13 yrs.	Retroperitoneal	8 mos.	Abdominal mass, pallor, anemia	Liver, bones
48118 Scott	F	10 wks.	Suprarenals	2 wks.	Abdominal mass, jaundice	Liver
48086 Scott	F	21 mos.	Right suprarenal	9 days	Abdominal mass, fever	Right kidney, lymph nodes
48120 Scott	M	7 yrs.	Left suprarenal	11 mos.	Hematuria, swollen abdomen	Kidney ?
48122 Scott	F	8 mos.	Suprarenal	.....	.....	.....
51140	M	4 yrs.	Suprarenal	4 mos.	Enlarged liver, blindness, retroperitoneal mass	Liver and skull

TABLE 1.—*Data on Cases of Neuroblastoma at the Harriet Lane Home, Johns Hopkins Hospital—Continued*

Path. No.	Sex	Age	Site	Duration	Symptoms	Metastases
			Suprarenal Neuroblastomas in Adults			
47146 Marten	M	45 yrs.	Suprarenals	3 mos.	Sacro-iliac pain following trauma	Lumbar vertebrae, bones, brain, lungs, lymph glands, suprarenals
A- 1094 U-15402	M	38 yrs.	Left suprarenal	9 mos.	Pain, nausea, right upper quadrant, chills and fever; diagnosed pyelitis	Liver, lungs, retroperitoneal nodes
43405 A-10476 U-16897	F	64 yrs.	Right suprarenal	2 mos.	Dyspnea, abdominal tumor, fever	Liver, retroperitoneal nodes, right kidney, all bones
A-2928 Bay View 103-1907	M	59 yrs.	Left suprarenal	.....	.....	Liver, right kidney, all nodes
49168 Jaisohn	M	32 yrs.	Suprarenal	2 wks.	Abdominal pain, nausea, vomiting	Peritoneal nodes
51092	M	40 yrs.	Suprarenals	.....	Axillary mass, pneumothorax	Pancreas, axillary nodes, brain and meninges

TABLE 2.—*Data on Extrasuprarenal Neuroblastomas*

Path. No.	Sex	Age	Site	Duration	Symptoms	Metastases
47272 Bergstrom	F	21 yrs.	Nose and forehead	8 mos.	Slowly growing nodule in center of forehead; erosion of bone and connection with nasal cavity	Extension, none in 1933
48090 Scott and Palmer	M	22 mos.	Thoracic cavity	6 wks.	Coughing attacks, fever, dyspnea, consolidation of right side of chest	Vertebra, spinal canal
51870	M	10 yrs.	Rib	1 mo.+	Lesion in rib	

neuroblasts, neurocytes, sympathicoblasts and sympathogonia) have been given to these small cells. These predominate in all the neuroblastomas occurring in infancy. Among these small cells are larger round cells with vesicular nuclei and carrot-shaped or pear-shaped cells resembling young spongioblasts. These elements are more or less constant and have their origin in the undifferentiated parent cells, forming the sympathetic nervous system. The different forms indicate a differentiation to the ganglion and chromaffin cells. The large ganglion and chromaffin cells of the ganglioneuroma and paragangliomas have in rare instances been found in the neuroblastoma. Occasionally masses of glia-like fibers are found. These occur more frequently, however, in the more highly differentiated paraganglioma.

The following case occurring in an adult shows microscopically a more mature types of cells.

Neuroblastoma of the Medulla of the Suprarenal Gland and Retroperitoneal Space Occurring in an Adult.—A white man, aged 45, suffered a jar as the result of the backfiring of a steam shovel. During the next five weeks the pain in the

Fig. 8 (path. no. 47146).—Roentgenogram of the spine in a case of neuroblastoma occurring in a white man, aged 45. The transverse process of the fourth lumbar vertebra has been eroded by the tumor mass which is invading the body of the vertebra.

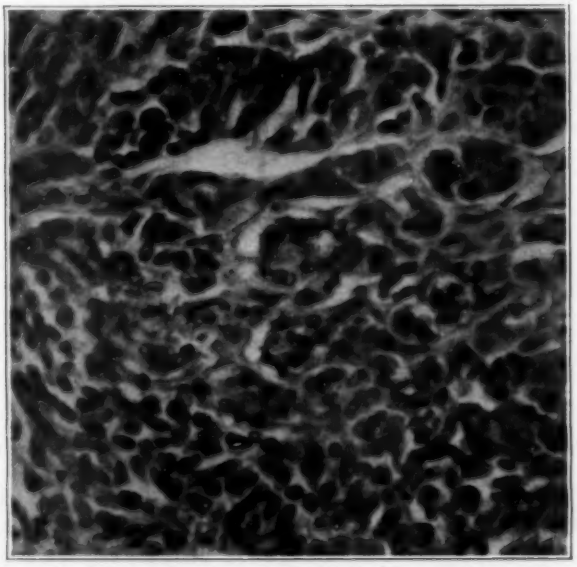

Fig. 9 (path. no. 47146).—Photomicrograph of the tumor in the patient shown in figure 8. The structure varies from the small cell neuroblastoma with intermediate spindle cell forms toward the paraganglioma type. To the left are seen the mixed spindle and round cells, and in the upper right-hand corner, cells with an increased amount of cytoplasm are arranged in an alveolar fashion.

left sacro-iliac region was so great that the patient became bedridden. Two months later a body cast was applied. This was removed in two weeks. When the cast was removed the pain became more severe and radiated up the left erector spinae muscle. Occasionally it radiated to the costal margin.

Physical examination revealed râles at the bases of both lungs and, in addition, dulness on the right side of the chest. Movement of the hip joints caused extreme pain, referred to the lumbar region. The right upper eyelid was edematous and slightly red. A large soft tumor mass later developed in the left axilla. A fracture of the body of the fourth lumbar vertebra was found on roentgen examination. A positive Kernig sign was also noted.

A roentgenogram of the spine showed changes in the bone in the first and fourth lumbar vertebrae. To the left of the fourth lumbar vertebra a hazy, round shadow could be made out. This had apparently eroded the transverse process and partly destroyed the body of the vertebra. The body of the first lumbar vertebra was collapsed. It had a mottled appearance, due to resorption of the bone and formation of new bone. A roentgenogram of the chest revealed a large mediastinal mass and metastases in the lower right lobe. A roentgenogram of the skull suggested beginning rarefaction in the frontal bone on the left side.

An autopsy was performed when this patient died. The clinical findings were then verified and a microscopic diagnosis made (figs. 8 and 9).

PARAGANGLIOMAS

Paragangliomas are the most common tumors of the sympathetic system and present many variations. Although more common than the neuroblastomas or ganglioneuromas, the pathologic process is less well defined than is that of the other two groups. One reason for this is the lack of agreement among anatomists as to what should be included in the chromaffin system. Kohn, in 1902, grouped the carotid body, the gland at the bifurcation of the aorta, the medulla of the suprarenal gland and the vertebral sympathetic ganglions into the chromaffin system on the basis of their reaction to potassium bichromate. Maximow raised some objections to this classification because the physiology was so different. He suggested, however, that certain cells of the liver, testis and heart should be included in the chromaffin system.

Regardless of difference in function and widespread distribution of chromaffin tissue, the tumors under discussion have common characteristics. The paraganglioma or chromaffin tumor most frequently encountered in the medulla of the suprarenal gland, the carotid body, the submucosa of the appendix and small intestine and the ganglions along the sympathetic nerves is a slowly growing tumor. These tumors are usually solitary and benign, but they may be multiple and malignant. The histologic picture may be so bizarre and variable that it may be difficult to distinguish some of the malignant paragangliomas from highly malignant carcinomas or sarcomas containing numerous tumor giant cells. This is another reason why the pathologic process has not been definitely established.

Fifty-two paragangliomas have been studied. Raiford, in a paper which recently appeared, discussed some which occurred in the gastro-intestinal tract. It is believed that these tumors are more widely distributed than is generally thought. The malignant paraganglioma may develop in any of the outlying sympathetic ganglions, and while the cells of such a tumor may resemble the chromaffin cells, they may also resemble the preganglionic type. Malignant paragangliomas and malignant ganglioneuromas may present similar histologic pictures. Many of the highly anaplastic and malignant carcinomas and sarcomas heretofore unclassified as to type and origin should in all probability be placed in this group. Many questionable xanthosarcomas, liposarcomas, hypernephromas and giant cell sarcomas are probably malignant paragangliomas or preganglionic sarcomas.

The two best examples of the paraganglioma are the tumors of the carotid body and the chromaffin tumor of the suprarenal gland (pheochromocytoma). The largest group are the argentaffin tumors (carcinoids) of the gastro-intestinal tract.

PARAGANGLIOMAS OF THE CAROTID BODY AND SYMPATHETIC STRUCTURES IN THE NECK

Tumors of the carotid body are the most representative of the paraganglioma group. They are composed of well defined cell nests marked off by a delicate stroma, characteristic of the argentaffin or carcinoid tumors of the gastro-intestinal tract. Again they may present numerous syncytial masses and a tendency to peculiar giant cell formation so characteristic of the paraganglioma of the suprarenal gland. Even in the benign tumors of the carotid body small lymphocytoid cells with deeply-staining nuclei and small carrot-shaped spindle cells indicate the relationship between these tumors and the more primitive and malignant neuroblastomas (Sullivan and Frazer's malignant tumor of the carotid body was a neuroblastoma). Malignant tumors of this type will contain cells of the preganglionic type.

Despite the well recognized clinical and pathologic features of this group, it is not definitely established that all paragangliomas in this region of the neck develop from the carotid body. In a case observed by Sheehan and Rabiner the tumor was embedded in the parotid gland, but was connected by a strand of tissue to the carotid at its bifurcation. In one of the cases in our series the tumor developed in the substance of the parotid gland and invaded the sheath of the facial nerve. In another of our cases the tumor was embedded in the thyroid. Rankin and Welbrock reported a case in which a tumor of the carotid body was diagnosed by section after a thyroidectomy had been performed for an adenoma.

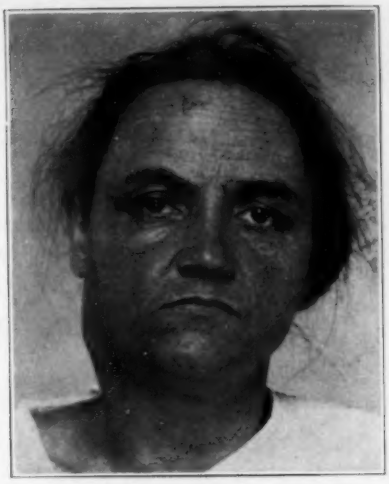

Fig. 10 (path. no. 24660).—A woman, aged 37, with a tumor of the carotid body of four years' duration. The tumor was unaffected by radium treatments but was successfully removed at operation.

Fig. 11 (path. no. 24385).—Photomicrograph of a typical tumor of the carotid body occurring in a man, aged 52, who had had a pulsating tumor in the left side of his neck for five years. The distinct alveolar structure of the tumor is emphasized. In the predominating cell, the character of the stroma and the small groups of neuroblasts the growth resembles the paraganglioma of the suprarenal gland shown in figure 2.

The age limits are between 7 and 68. The usual age is between 35 and 50. All the cases in our series were in adults. The long history (from one to thirty-five years in our series and from two to fifteen years, according to Rankin and Welbrock) indicates the benign character of the majority of these lesions.

TABLE 3.—*Paragangliomas of the Carotid Body*

Path. No.	Sex	Age	Site	Duration	Symptoms	Metastases
50825	M	45	Bifurcation, carotid artery	12 yrs.	Lump gradually increasing in size, 3 cm. in diameter; adherent to deep structures	Possible recurrence
44444	M	53	Lateral portion, thyroid	1 yr.	Rapidly growing mass in left side of neck, somewhat cystic and deeply attached	Mediastinal lymph nodes involved
35408	M	67	Parotid gland	25 yrs.	Gradual extension of facial paralysis	Extension; recurrence, death
29007	M	30	Bifurcation, carotid artery	5 yrs.	Painless lump in left side of neck; gradual enlargement	None
24660*	F	37	Bifurcation, carotid artery	4 yrs.	Stinging pain and throbbing in right side of neck; nodular, fixed growth	None
24385	M	52	Bifurcation, carotid artery	5 yrs.	Pulsating tumor in left side of neck, diagnosed aneurysm; coughing	None; extension
31826*	M	46	Bifurcation, carotid artery	5 yrs.	Pulsating tumor in left side of neck, extending from lobe of ear to within 3 cm. of clavicle; thrill over the tumor; blood pressure 160; large and expansile	None
33032*	M	47	Bifurcation, carotid artery	35 yrs.	Swelling in right side of neck; ptosis of right upper eyelid and constriction of right pupil; paralysis of right vocal cord	None
23130	M	Adult	Lymph node, neck	.....	Biopsy	
19723	M	Adult	Lymph node, neck	.....	Biopsy	Dead
40669	F	65	Lump in neck	4 yrs.	Firm mass in left side of neck	Metastases to lymph nodes
50825	M	45	Swelling in neck	7 yrs.	Lump in right side of neck gradually increasing in size	None
51579	F	42				

* These cases also reported by Reid, Mont. R.: Adenomata of the Carotid Gland, Bull. Johns Hopkins Hosp. **31**: 177 (June) 1920.

The following characteristics are of diagnostic significance: (1) position at the bifurcation of the carotid artery; (2) long duration of symptoms and slow growth; (3) expansile pulsation, bruit and thrill, suggestive of aneurysm, but no other changes in spite of long duration; (4) oval character of the swelling, and mobility laterally; (5) tendency of the growth to bulge into the pharynx without causing ulcerations of the mucous membrane, and (6) failure to respond to radiation.

One of the most interesting clinical findings is the expansile pulsation. A tumor of the carotid body may resemble closely a carotid aneurysm, but there are no cutaneous or other changes even after the tumor has been present for a number of years. Lateral without vertical mobility is an important differential point.

Paraganglioma of the Carotid Body.—A Negro, aged 45, noticed a small lump near the angle of the jaw five years before admission. This had grown steadily from the size of a walnut to that of a man's fist. No pain or tenderness was noted. No history of difficulty in swallowing was elicited when the history was taken.

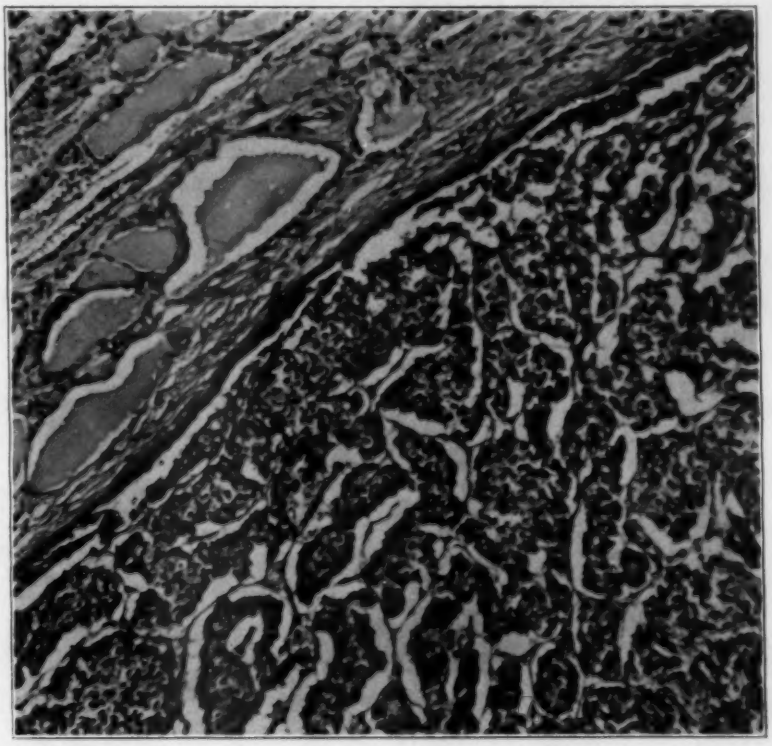

Fig. 12 (path. no. 44444).—Paraganglioma of the thyroid gland occurring in a white man, aged 54, and metastasizing to the mediastinum and liver. The photomicrograph shows an area of typical paraganglioma compressing normal thyroid tissue. Another area of this tumor (fig. 14) was distinctly malignant. This benign area should be compared with that shown in figures 2 and 11.

Physical examination revealed a large oval mass about 10 cm. long, which extended from the angle of the jaw on the right side to the clavicle. The mass was lobulated and firm. It was adherent to the underlying structures, but not to the skin. A definite expansile pulsation was present, and a bruit or swish could be heard during systole. A widened mediastinal shadow could be made out

on roentgen examination, and the mass in the neck was thought to be continuous with the mediastinal mass. The mass was explored, and the patient died on the table from respiratory failure.

At autopsy the heart was found to be greatly enlarged. In the mediastinum was a smooth mass measuring 8.5 by 6 by 3 cm. It was soft, but not fluctuant. On the right side of the neck was a mass measuring 9 by 10 by 8 cm., which

Fig. 13 (path. no. 24460).—Tumor of the carotid body of the benign paraganglioma type with distinct areas of neuroblastoma (patient shown in fig. 10). The photomicrograph shows epithelial-like paraganglioma cells in the upper portion of the picture with small deeply staining neuroblastoma cells in the lower portion. The section illustrates the cycle of development from embryonic neuroblasts to a more adult chromaffin tissue, typical of all paragangliomas of the sympathetic system.

surrounded the bifurcation of the carotid artery. At the upper pole of the mass were three enlarged lymph nodes. The carotid artery bifurcated at the center of the mass. The mass did not invade the jaw or salivary glands, but pressed against

the trachea. On microscopic examination the mass presented a definite alveolar structure, the epithelial cells tending to be arranged in syncytial masses. The mass in the mediastinum was inflammatory. A definite syphilitic aortitis was demonstrated and definite tubercles were found in the lungs and liver.

Paraganglioma Occurring in the Thyroid Gland; Possibly Connected with the Carotid Body.—A white man, aged 45, began to have trouble with his neck a year before admission to the hospital. A tickling sensation was first noted, and shortly afterward a small lump about the size of the end of the thumb developed. This

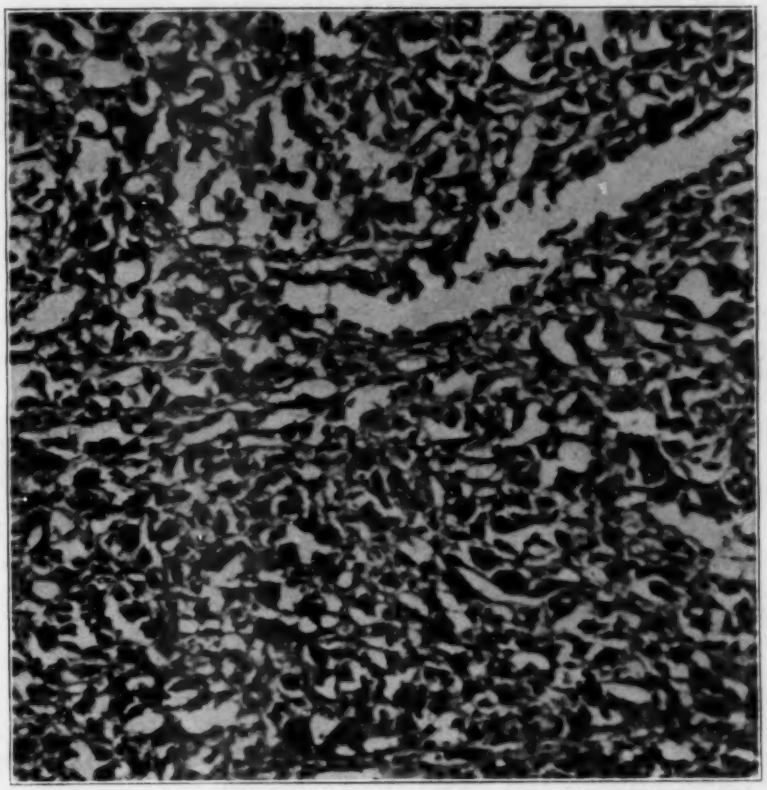

Fig. 14 (path. no. 44444).—Area of malignant paraganglioma invading the thyroid taken from the section shown in figure 12. The photomicrograph illustrates the tendency of these tumors to differentiate toward chromaffin and ganglionic structures.

mass had steadily increased in size. There had been no difficulty in swallowing or breathing.

On examination the mass appeared to be in the right lateral lobe of the thyroid. The trachea was pushed to the left and the mass, which was round and slightly movable, seemed soft but not definitely cystic. Tenderness was noted in the flank on the same side, but no definite tumor could be palpated in the region of the right kidney. The patient had no exophthalmos. The basal metabolic rate was 33.

An operation was performed on Feb. 14, 1931. A mass was removed from the region of the right lobe of the thyroid. On the left this mass extended well over the trachea. On the right it extended back to the vertebrae. The capsule was ruptured when the tumor was removed. Several enlarged lymph nodes extended from the thyroid down into the mediastinum. On gross examination these nodes seemed to be the seat of metastatic growths. The patient died in 1932 with metastases to the liver and mediastinum.

The tumor was reddish yellow and had small cystic areas. To one portion of the tumor was attached a small strip of thyroid tissue. Frozen sections showed that the mass was probably carcinomatous, and that the lymph nodes were involved. Large epithelial cells were found in the lymph nodes. Microscopic

Fig. 15 (path. no. 35408).—Paraganglioma involving the parotid gland in a white man, aged 67. The photograph was made after two recurrences and before the third operation. Death occurred two months later. The tumor is below the ear and between the scars of the two previous operations.

examination revealed two distinct types of tissue. One had a typical alveolar arrangement (fig. 12), the usual histologic appearance of a benign paraganglioma of the carotid body, and other sections appeared sarcomatous, many large malignant spindle cells, tumor giant cells and immature ganglion cells being found (fig. 14).

Paraganglioma of the Parotid Gland.—A white man, aged 67, had had two operations when first seen at the clinic and five treatments with the roentgen rays. The original trouble dated back twenty-five years when he discovered a lump just below his right ear. This was removed, but recurred. An operation was performed in 1914. At the second operation there was thought to be a cyst of the parotid gland. It was attached to but not embedded in the parotid gland. A recur-

rence was noted in a few years, and another operation was not advised. In 1923 neuralgic pains were noted at the site of the recurrence. Facial palsy later developed.

At the time of examination in May, 1924, a definite facial palsy was noted. The tumor extended from beneath the lobe of the ear on the right side, behind the angle of the jaw to the region of the mastoid. No enlarged lymph nodes were found. The hemoglobin was 80 per cent and red and white cell counts were normal.

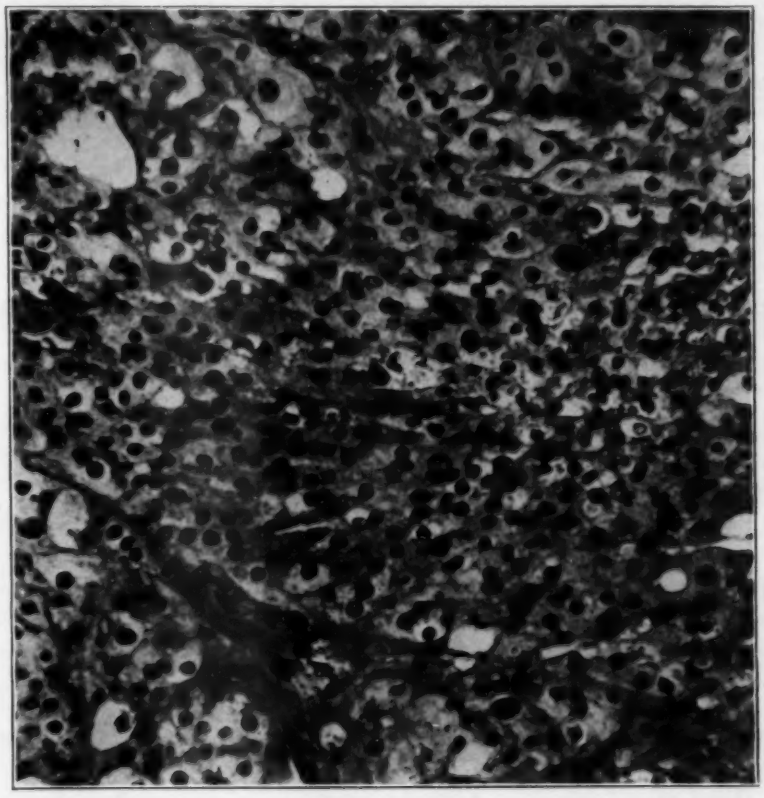

Fig. 16 (path. no. 35408).—Photomicrograph made from the section of tumor shown in figure 15. Epithelial cells with a large amount of cytoplasm are forming syncytial masses. There are numerous large malignant-looking nuclei. Among these epithelial cells there are smaller cells resembling neuroblasts. The stroma of the tumor divided the growth into lobules, typical of those found in the more benign paragangliomas.

At operation, performed on May 29, 1924, the parotid gland was completely removed, with some of the sternocleidomastoid, a segment of the internal jugular vein and branches of the facial nerve. The external carotid artery was ligated. In removing the mass, a cyst was ruptured. The patient was reported dead on July 29, 1924.

The gross specimen consisted of a mass measuring 6 by 3 cm. On section there were two cysts in which soft brown tissue was found. This was adherent to the wall of the cyst. Microscopically, the tissues had a definite alveolar structure (figs. 15 and 16). Epithelial cells with heavily staining nuclei and a fair amount of cytoplasm predominated. Among these cells were a few tumor giant cells. In most areas the borders of the cytoplasm were indistinct.

PARAGANGLIOMAS OF THE MEDULLA OF THE SUPRARENAL GLAND

Over fifty reports of chromaffin tumors of the medulla of the suprarenal gland have appeared in the literature. Most of the tumors have been solitary and benign; a few, bilateral and malignant. Similar tumors have been described in the retroperitoneal tissue about the suprarenal gland, in the coccygeal gland and in the sympathetic ganglions. Manasse (1893) is given credit for the first description. Marchetti (1904) described the first bilateral case. Suzuki (1910) recorded a case associated with neurofibromatosis, and Laignel-Lavastine and Aubertin a case associated with melanoderma. Neusser and Wiesel (1910) first emphasized that vasomotor instability and vascular changes might develop during the clinical course. Helly (1913) directed attention to paroxysmal hypertension, and Riemer (1928) reported a case associated with Addison's disease and hypotension.

Eisenberg and Wallerstein, in a recent review came to the conclusion that there is no significant relationship between these chromaffin tumors and hypertension. The tumors occurred with equal frequency in the sexes. They appeared most frequently in the fifth decade, the age limits being 2½ and 82 years. According to these authors, in only five of the reported cases were the tumors malignant, and in all of these both suprarenal glands were involved. They emphasized among the histologic features the great variability in the size and shape of the cells and their nuclei, the chromaffin reaction and the vascularity. Although Eisenberg and Wallerstein noted the relationship between these tumors of the suprarenal gland and those arising from retroperitoneal chromaffin tissue and the tumors of the carotid body, they made no mention of a similarity between these and the argentaffin tumors (carcinoids) of the intestinal tract.

Like the tumors of the carotid body, the paragangliomas of the suprarenal gland are practically confined to adult life. They may be associated with definite and varied clinical manifestations. In but one case was the tumor accidentally found at autopsy without a previous history of definite symptoms. Hypertension, hypotension and vasomotor instability are most frequently noted. Twenty-five of the patients had definite hypertension. One each had Addison's syndrome, vasomotor instability or fainting attacks. Another common finding is multiple neurofibromatosis or Recklinghausen's disease. This was recorded

in six cases in the literature. Diabetes or glycosuria occurred in five, and in three there were lesions of the thyroid, either a simple or a malignant goiter.

Most of the cases of paraganglioma of the suprarenal gland recorded since 1910 have been studied by pathologists and most have been found in adults who had definite hypertension. Hypertension occurring in these cases is now, however, regarded as incidental in most instances. The histologic feature of these growths in the suprarenal gland and retroperitoneal chromaffin tissues may vary a great deal. Many tumors which were formerly called hypernephromas and unclassified retroperitoneal sarcomas are now classified as paragangliomas. The microscopic picture of the malignant paraganglioma of the suprarenal gland is repro-

Fig. 17 (path. no. 47632).—Malignant paraganglioma of the suprarenal gland occurring in a woman, aged 34, and metastasizing to the retroperitoneal nodes. The specimen shows the tumor mass in the suprarenal gland and about the upper pole of the kidney, invading the renal cortex at one point. With the exception of this area the nodules of the tumor are encapsulated.

duced at times by tumors developing from the sympathetic nervous tissue in the extremities and in different viscera.

Urinary symptoms may be caused by these tumors, and a deformity of the renal pelvis may be found in the pyelogram. This deformity is caused by pressure rather than invasion. Some cases, because of involvement of the lower dorsal and lumbar portion of the spine, may begin with sciatica. Gastro-intestinal symptoms predominate in some cases because of secondary involvement of the intestines or metastases to the liver. Hypertension has been noted in some cases. Glycosuria may result from hypersuprarenalemia due to excessive secretion by the tumor. In the cases in which the symptoms of Addison's disease and melanoderma have been noted, the suprarenal cortex has been

destroyed by the tumor. The syndrome of Addison has been reported when the tumor has been unilateral and the other suprarenal has been normal. As more cases are reported, it is found that these tumors have a decided tendency to form visceral and skeletal metastases.

TABLE 4.—*Data on Paragangliomas*

Path. No.	Sex	Age	Site	Duration	Symptoms	Metastases
Paragangliomas of the Suprarenal and Retroperitoneal Spaces						
47632 36525	F	34	Suprarenal	1 yr.	Constipation, night sweats; mass in upper left part of abdomen; 12/29/30, nephrectomy	Kidney, retroperitoneal nodes
46958	F	53	Left kidney, suprarenal	6 mos.	Pain, hematuria; left kidney displaced down in pyelogram; 1929, excision	None
46954 Wallerstein	F	55	Right suprarenal	1 mo.	Biopsy	Autopsy: bones, viscera, lung, etc.
46650	M	40	Left suprarenal	.....	Suicide, antimony poisoning	None
43558 I. Cohn	M	51	Left suprarenal	1 mo.	Epigastric distress; laparotomy bilateral March, 1930	Neighboring lymph nodes
37091	F	66	Kidney			
33598	M	..	Suprarenal			
29397	M	28	Retroperitoneal and lumbar region	12 mos.	Femur, spine, os calcis, joint and bone pain; amputation of os calcis 12/27/20	
Extrasuprarenal Paragangliomas						
49133	F	43	Right breast	5 mos.	Rapid growth, size of grapefruit; mass in right breast; amputation 3/16/31	Lung, pleura, skin
47860	M	63	Arm	3 yrs.	Subcutaneous tumor; excised, 1929; recurred, 1932	
28117	M	17	Tibia	6 wks.	Trauma and pain; amputation, June, 1916; excision of glands in groin	Regional lymph nodes
12324 Aut. No.	M	61	Upper part sternum	7 yrs.	Pain and swelling; excision, 12/10/31	Invasion of lung

The histories which follow indicate the characteristics of malignant paragangliomas:

Malignant Paraganglioma (Retroperitoneal).—A Negress, aged 36, was first seen in October, 1924, at which time she complained of a lump in the upper right side of the abdomen. The mass was not tender. It extended back to the lumbar region. A pyelogram was made. This revealed a deformity of the right renal pelvis. The phthalein excretion was 25 per cent in two hours. The nonprotein nitrogen was 30 mg. per hundred cubic centimeters. An exploration of the right lumbar region was made on June 18, 1931. A large tumor which was adherent

to the diaphragm and occupied the region of the kidney was found. Most of the tumor was above the kidney. The tumor could not be removed. A section was taken. The patient died six days after the operation. Consent for an autopsy could not be obtained.

Microscopic studies revealed a malignant tumor. Epithelial cells predominated, among which were found an occasional large ganglion cell and many malignant tumor giant cells. The predominating cells were those of the preganglionic type.

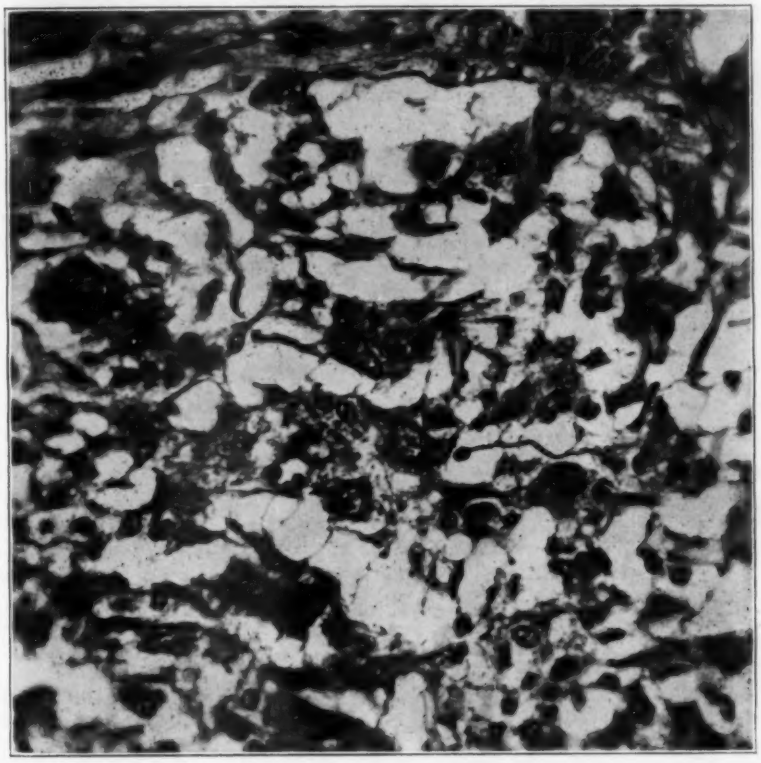

Fig. 18 (path. no. 46650).—Highly differentiated paraganglioma of the medulla of the suprarenal gland with large syncytial giant cells. This tumor was found accidentally at autopsy and did not involve structures beyond the medulla of the suprarenal gland. Although clinically benign, there were many nuclei of malignant appearance. The tumor bears a remarkable resemblance to the normal medulla of the suprarenal gland.

Malignant Paraganglioma of the Lumbar Retroperitoneal Region.—A white youth, aged 20, had had a recurrent dislocation of the left shoulder. This was operated on in May, 1921. In September of the same year the patient complained of a severe pain in the right thigh. In a roentgenogram of the spine a lesion of the fourth lumbar vertebra was found. The lesion was at the side of the vertebra, and the transverse process was eroded. This lesion was at first thought to be tuberculous, and a Hibbs' operation was performed on September 23. Following

this a swelling appeared in Petit's triangle, which was aspirated. A roentgenogram was again made and it was found that the mass had extended to the sacrum below and to the first lumbar vertebra above. The patient died on November 27.

Roentgenograms taken post mortem showed areas of destruction in the cervical and lumbar spine, nodules in the ribs and in both humeri and femurs. Roentgenograms of the skull were negative.

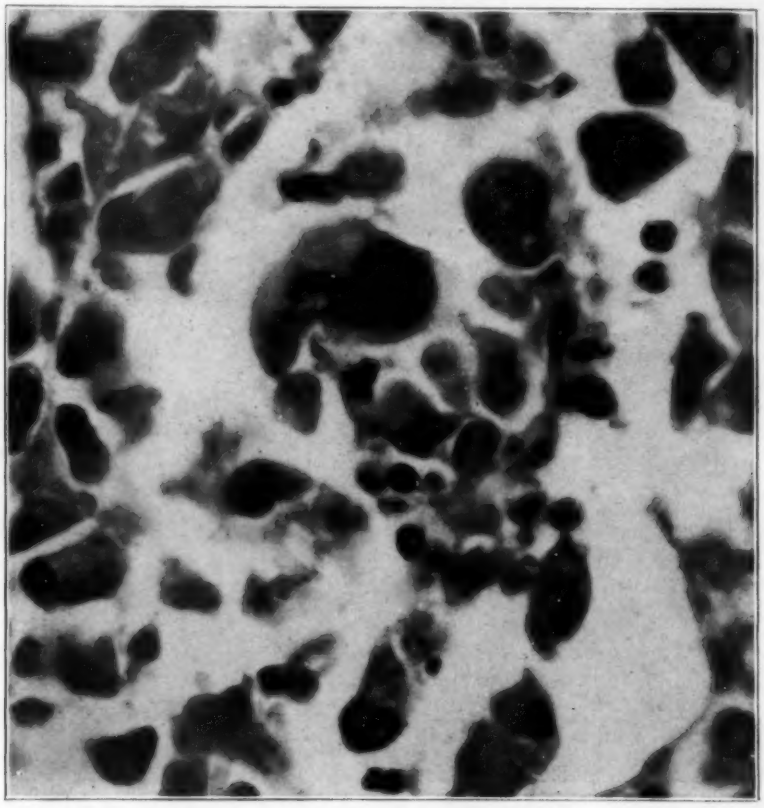

Fig. 19 (path. no. 46954, case of Dr. Eisenberg and Dr. Wallerstein).—Malignant paraganglioma of the suprarenal gland metastasizing to the gums, skeleton and visceral organs in a white woman, aged 55. The photomicrograph shows the large preganglionic cells and smaller neuroblasts among the more moderate-sized chromaffin cells of the paraganglionic type.

At autopsy three distinct tumor masses were found. An enormous mass was found in the lumbar region. Another elongated mass 1 inch in length which had the appearance and feeling of firm butter was found at the level of the second dorsal vertebra. The third mass was anterior to the second cervical vertebra and was similar in appearance to the second growth. The large lumbar mass was soft and fluctuant. The body of the second lumbar vertebra was entirely resorbed. The suprarenal glands were normal on gross examination. No other tumor masses

were found. All the viscera appeared normal. The tumor was composed of epithelial masses surrounded by a loose and delicate stroma. Many of the nuclei were large and had the appearance of those of a malignant tumor. At the margins the tumor resembled a typical tumor of the carotid body. In other parts of the section many small spindle cells with dense nuclei, such as occur in a neuroblastoma, were found.

Pathology.—Paragangliomas of the suprarenal gland rarely attain large size. The small tumors are solid; the larger, more often cystic and hemorrhagic. They are usually definitely encapsulated, yellowish and mottled red. The smaller tumors are surrounded by a rim of compressed suprarenal cortex.

These tumors have an alveolar structure, but the cell grouping is more regular than that of the tumors of the carotid body (fig. 2). The cells vary markedly in size, the cuboidal and polyhedral forms of moderate size predominating. In paragangliomas of the suprarenal gland there is a tendency toward syncytial formation. In the malignant forms giant, atypical ganglion and large spindle cells are found. Malignant paragangliomas are remarkable because of the size and variety of the giant cells. Eisenberg and Wallerstein have said that the greatest imaginable irregularity in the size and shape of the cells and nuclei is the most striking histologic feature.

The epithelial cells, when freshly stained with chrome salts or when fixed in Zenker's solution, show pigmented granules. After prolonged fixation in formaldehyde the cytoplasm will stain deeply with hematoxylin, a characteristic also of the cells of the normal medulla of the suprarenal gland.

ARGENTAFFIN TUMORS OR PARAGANGLIOMAS OF THE GASTRO-INTESTINAL TRACT

In 1910, Huebschamm, after studying a group of small and slowly growing tumors of the appendix and intestine, came to the conclusion that the growths developed from cells belonging to the chromaffin system. Oberndorfer had before separated these tumors from appendical carcinoma and had given them the name carcinoid. The work of Masson supported the contention of Huebschamm as to the chromaffin origin of these tumors. These tumors are now regarded as paragangliomas.

These tumors occur twice as frequently in the appendix as in the small intestine, and are relatively rare in the large bowel. Over three hundred cases of this tumor of the appendix have been reported. Over one hundred have occurred in the small intestine, and cases of these tumors in the stomach, large bowel and rectum have been recorded. Raiford recently reported twenty-nine cases from the Surgical Pathological Laboratory of Johns Hopkins Hospital. At the time this paper

was written this number had increased to thirty-five. Twenty-two of the tumors have occurred in the appendix, ten in the small intestine, two in the large bowel and one in the stomach.

As in other paragangliomas, the tumors of the gastro-intestinal tract occur usually in adults. The extreme ages in our series are 12 and 66 years. Symptoms appear earlier when the appendix is involved and the average age is less than when the tumor develops in the intestine. The symptoms of appendical carcinoids are suggestive of appendicitis, and not infrequently when an operation is performed for appendicitis a

Fig. 20 (path. no. 47648).—Gross specimen of a typical argentaffin tumor situated in the end of the appendix. The lumen of the appendix is compressed but not invaded by the tumor tissue.

paraganglioma is found. When the tumor occurs in the intestine, diarrhea without melena is common. The symptoms are often due to an incomplete obstruction of the lumen of the appendix or intestine.

The majority of these growths are benign and run a slow course. About 20 per cent undergo malignant changes. Eight of the cases in our series were malignant, metastases forming in the lymph nodes of the mesentery, in the glands about the aorta and in the liver. In the malignant cases acute obstruction may develop. Argentaffin tumors of the small intestine become malignant more frequently than do those of the appendix.

Fig. 21 (path. no. 48429).—Argentaffin tumor (carcinoid) involving the cecum in a woman, aged 46, with abdominal symptoms of two weeks' duration. The photomicrograph shows the islands of epithelial-like structures typical of all the benign paragangliomas. Among these islands and toward the lower portion of the pictures groups of small deeply staining cells arranged in rosettes are seen. The cycle of growth illustrated is from the small neuroblastic tissue to the larger masses of cells of a chromaffin nature. Metastases were present in the regional mesenteric nodes. The patient has remained well for three years following resection.

The prognosis of paragangliomas of the intestine is good. Four of eight patients in whom the lymph nodes were affected have remained well. In the fatal cases metastases have formed in the liver.

Paraganglioma of the Cecum with Involvement of Lymph Nodes.—History.—A. B., a white woman, aged 46, was admitted to the hospital on Oct. 20, 1930,

TABLE 5.—*Data on Carcinoid or Argentaffin Tumors*

Path. No.	Sex	Age	Site	Duration	Clinical Course	Metastases
				Stomach		
40700	M	55	Stomach	10 mos.	Vague attacks of indigestion with nausea and vomiting; tenderness; laparotomy; inoperable	Liver, lymph glands
				Small Intestine		
48536	M	47	Ileum	18 mos.	Intermittent abdominal pains, intestinal obstruction; resection, 5 ft. of ileum	Mesenteric gland
36786	M	49	Duodenum	6 wks.	Pain in abdomen, vomiting; excision of small tumor nodule	None
31805	F	45	Jejunum	.....	Resection, 3 cm. of small intestine	Aortic glands
G-10048	M	57	Ileum	.....	Respiratory symptoms; autopsy	Liver, regional glands
G-10023	F	44	Ileum	2 days	Acute pain, nausea and vomiting; appendectomy	None
G- 8875	M	62	Ileum	6 wks.	Pain in right hip and thigh following ununited fracture of neck of femur; autopsy	None
G- 6739	M	50	Jejunum	1 yr.	Gastric obstruction, loss of weight; exploratory laparotomy; inoperable	None
G- 4110	F	66	Ileum	7 wks.	Tenderness, umbilical hernia; rapid growth; exploratory laparotomy	None
G- 3880	M	60	Ileum	2 wks.	Dyspnea and cardiac decompensation; autopsy	None
3676	M	55	Ileum	.....	Symptoms of acute lobar pneumonia; autopsy	None
				Appendix		
49704	F	26	Appendix	12 hrs.	Acute gastric distress, vomiting; appendectomy performed	None
49112	F	28	Appendix	5 mos.	Symptoms of appendicitis	None
48344	F	62	Appendix	5 mos.	Abdominal pressure and distress; both tubes and ovaries removed for papillary adenocarcinoma; routine appendectomy	None
48126	M	27	Appendix	.....	Abdominal distress; appendectomy	None
48124	M	60	Appendix, liver	.....	Abdominal symptoms; plaques under liver, masses along root of mesentery; biopsy performed	Liver, mesenteric glands
47648	F	41	Tip	.....	Indefinite pain; appendectomy	None
47522	F	16	Tip	.....	Dull pain; anorexia, nausea and vomiting; tenderness; resection, cecum, terminal ileum and appendix; ileocolostomy	Cecum and ileum
47322	F	15	Tip	4 days	Pain, vomiting, nausea, tenderness; appendectomy	None
47168	F	28	Tip	.....	Pain in side, abdomen and back, accompanied by nausea and vomiting; right oophorectomy and appendectomy	None
46846	F	14	Tip	4 days	Pain, nausea and vomiting appendectomy	None

TABLE 5.—*Data on Carcinoid or Argentaffin Tumors—Continued*

Path. No.	Sex	Age	Site	Duration	Clinical Course	Metastases
				Appendix—Continued		
46754	M	28	Tip	6 days	Intermittent nausea and vomiting with acute pain; appendectomy	None
43818	F	15	Tip	3 mos.	Indefinite symptoms of pain, nausea and vomiting; tenderness; appendectomy	None
43638	F	16	Tip	6 mos.	Pain, nausea and vomiting; appendectomy	None
42135	M	15	Base	18 hrs.	Severe pain and vomiting; tenderness; appendectomy	None
38799	M	23	Tip	1 mo.	Intermittent attacks of indigestion with pain, distention, vomiting, fever; tenderness; appendectomy	None
38053	M	22	Middle	2 days	Sudden continuous pain in right flank; tenderness and subnormal temperature; appendectomy	None
37636	F	28	Middle	.....	Appendectomy and suspension of uterus	None
34485	F	27	Tip	5 yrs.	Indefinite attacks of pain; severe attack day before admission; appendectomy and cholecystectomy	None
31301	F	33	Tip	.....	Pain, nausea and vomiting; appendectomy for acute appendicitis	None
21703	M	30	Tip	2 yrs.	Indigestion, intermittent pain; exploratory laparotomy; appendectomy	None
15978	M	12	Middle	2 wks.	Pain, hematemesis; mass in right side, one week; tenderness; exploratory laparotomy; appendectomy	None
G- 6032	F	64	Base	.....	Fall in street car; patient brought in coma; cerebral hemorrhage; autopsy	None
				Colon		
48429	F	46	Ascending colon	2 yrs.	Intermittent epigastric pain; vomiting, distention and diarrhea; resection of terminal ileum, cecum with lateral ileocolostomy	Glands of mesentery
G-10562	M	53	Sigmoid flexures	2 mos.	Nausea, epigastric distress; pain, loss of weight, anorexia; hard, nodular masses in abdomen; autopsy	Glands, liver, lungs

complaining of attacks of abdominal pain, distention and diarrhea. For several years she had been subject to attacks of dyspepsia which were variable in duration, intensity and periodicity. The present attack differed from the preceding only in its slightly greater severity. The only relevant detail in the past history of the patient was an attack of pulmonary tuberculosis twelve years before, from which she had apparently recovered entirely.

Physical Examination.—The patient was a well nourished white woman in no acute discomfort. A small mass was palpable in the right lower quadrant of the abdomen; this was about the size of a lemon, freely movable and not tender. Roentgenograms made following a barium sulphate meal showed a dilated terminal ileum but no evidence of a constriction. Following a barium enema, however, the

roentgenograms revealed a large constricting filling defect in the cecum. This was diagnosed as neoplasm, but in view of the past history of tuberculosis the possibility of an inflammatory mass was considered. An exploratory laparotomy was advised and accepted.

Operation (Nov. 6, 1930).—When the abdomen had been opened a hard and freely movable mass could be felt in the cecum. A few of the regional mesenteric glands were enlarged and hard, but in spite of this the tumor was thought to be operable. Accordingly, the operator resected the growth together with a V-shaped piece of mesentery containing the enlarged glands. A lateral anastomosis was then made, and the abdomen was closed. Some of the enlarged lymph nodes could not be removed because they were intimately related to the superior mesenteric artery.

The diagnosis was carcinoid or argentaffin tumor of the cecum with metastases to the regional mesenteric lymph glands.

Comment.—The first pathologist who examined the growth made a diagnosis of adenocarcinoma because of the numerous pseudo-alveoli in the edges of the tumor but largely because of the rarity of carcinoid tumors in the colon. The yellow color, however, is not typical of carcinoma. The microscopic arrangement of the cells, while not absolutely conclusive, is so typical that after observing a number of carcinoids one can hardly fail to identify the type even without recourse to special stains.

The gastro-intestinal history was extremely vague. As the condition extended over a number of years, it was practically impossible to ascertain the date of onset of the first relevant symptom. This suggests that the development and growth of the tumor were extremely insidious. It would be unwise to attempt the diagnosis of a carcinoid tumor from the clinical history alone, but a tumor mass characterized by an insidious onset of vague gastro-intestinal symptoms and unusual general symptoms previous to the formation of metastasis suggests a tumor of this type.

Course in Hospital.—The patient had a stormy postoperative convalescence complicated by the development of a fecal fistula on the fifteenth day after operation. This drained freely for a time and finally closed three months later. She was discharged improved and when last heard from (November, 1933, three years after operation) she was entirely well and had gained 37 pounds (16.8 Kg.).

Macroscopic Examination of Tumor.—The specimen consisted of a resected portion of bowel 6 inches (15.24 cm.) in length. In the center of this was seen an annular constricting tumor completely encircling the bowel but producing no elevation on the serosal surface. When the specimen was opened, it was found that the tumor had partially occluded the lumen. The growth had apparently originated in the submucosa but had involved the entire wall of the bowel secondarily. The mucosa was intact over the surface. The cut section was firm in consistency and yellow. Attached to the resected mesentery were several enlarged lymph glands. One of these was quite hard and when sectioned exhibited the same yellow color as the original tumor.

Microscopic Examination.—The tumor was composed of densely packed cuboidal cells arranged in strands and compact groups. These were fairly uniform in size and possessed a moderate amount of granular cytoplasm. These granules stained dark brown or black with the silver impregnation technic, identifying the tumor as one of the argentaffin type. Occasional vacuoles could be seen near the bases of the cells. The stroma was quite dense and surrounded the nests of the cells,

leaving them as discrete islands of tumor tissue. A hyperfibrosis accompanied the metastases, so that the normal structure was almost completely replaced by the tumor and its stroma.

GANGLIONEUROMAS

Virchow, in classifying tumors of the nerves, recognized the possibility of the development of a "neuroma gangliocellulare." The description of the first case of such a tumor was published in 1870. In that year Loretz reported a case, and between that date and 1901 ten cases were reported. Tumors were described in both the sympathetic and the central nervous system. Knaus has reported a case of multiple ganglioneuroma associated with Recklinghausen's disease. Beneke reported a

TABLE 6.—*Data on Ganglioneuromas*

Path. No.	Sex	Age	Site	Duration	Symptoms	Metastases
49816	M	28	Acoustic nerve	.....	Petrous portion of temporal bone removed at autopsy for routine study of ears	None
47692 Lee	F	15	Retroperitoneal, right suprarenal	1 yr.	Pain in right leg and right side of abdomen; amenorrhea	Skull
46806 Curtis	M	10	Cervical region	1 yr.	Painless mass above clavicle	None
40083	F	45	Right thigh	1 mo.	Painful, tender, aching mass; swelling and severe pain	Recurrence; dead
37512	M	4	Neck	?	Biopsy of glands of neck, 1926; enlarged and swollen	None; dead, 1927
27088 Watson	M	Adult	Midbrain	.....	Intracranial pressure; autopsy	None
21763	M	41	Cervical region	18 yrs.	Painless nodule in left side of neck	Lungs
6711	M	28	Finger	1 yr.	Nodular, hard, pulsating mass; edema of finger	None

case in which malignant changes occurred in a ganglioneuroma, in which large ganglion cells and smaller embryonic neuroblasts from which the ganglion cells probably developed were found. By 1914, Wahl was able to collect forty-seven cases of ganglioneuroma. Twenty-five of these occurred in females; in twenty-nine of the forty-seven cases the patients were less than 30 years of age, and in twenty-nine the tumor developed in the retropleural or retroperitoneal spaces.

CLINICAL FEATURES

Including the cases collected by McFarland (ninety-three) and those appearing in recent literature (Watjen, MacAuley, Alpers and Grant, Bergonzi, Jackson and Babcock, Guizzetti, Smirnow and Bischoff) together with eight in our series, the ganglioneuromas reported to date number one hundred and eleven.

Fig. 22 (path. no. 49816).—Low power photomicrograph of benign ganglioma occurring in the acoustic portion of the eighth nerve. The ganglioneuroma is indicated by the arrow and involves the nerve just before it enters the cochlea.

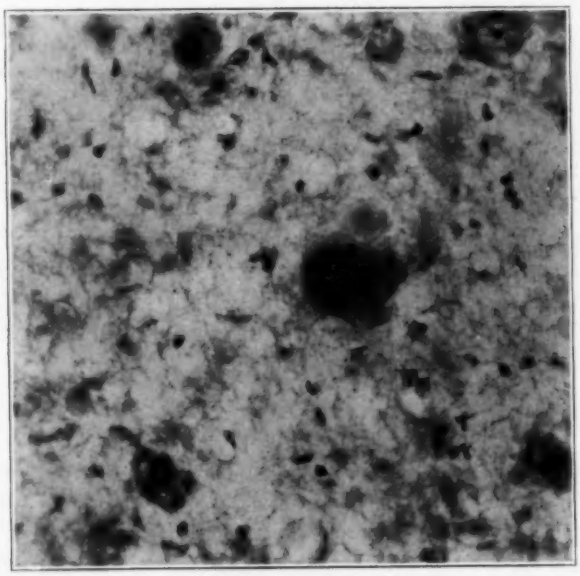

Fig. 23 (path. no. 49816).—High power photomicrograph of the tumor shown in figure 22. The large benign ganglion cells are embedded in the reticulated mass of neurogenic fibers.

These tumors are, as a rule, benign and solitary. They may be multiple and malignant, and may occur anywhere in the central or peripheral, as well as in the sympathetic, nervous system. In our cases variability in location and growth was striking. The age at which this tumor appeared varied from 4 to 45 years. Three developed in the

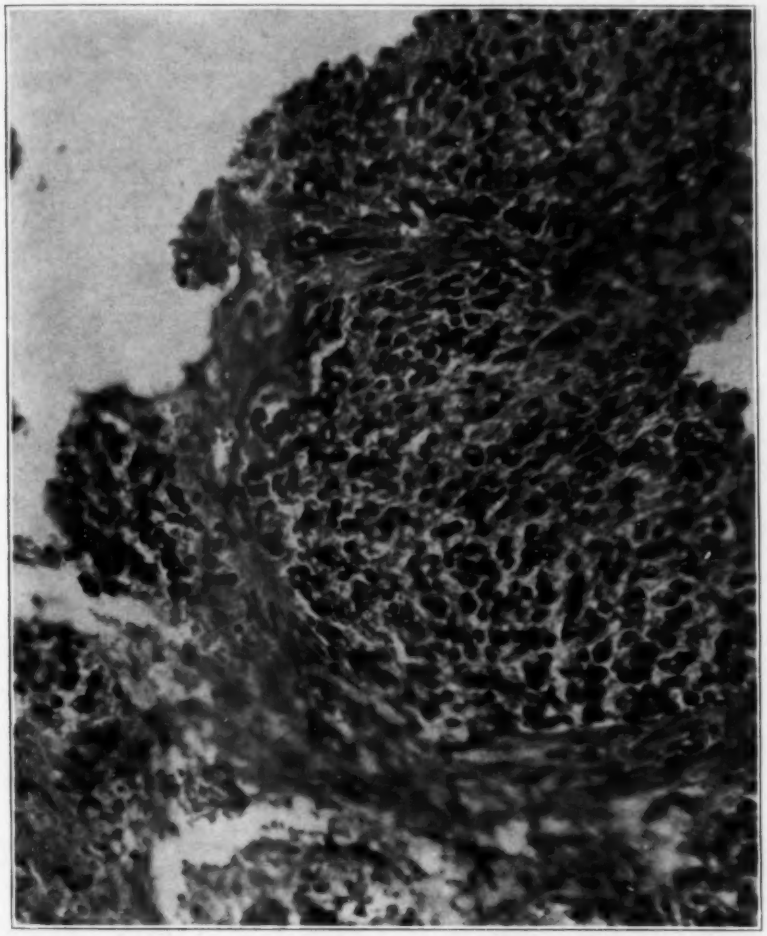

Fig. 24 (path. no. 47692).—Area of a malignant ganglioneuroma occurring in the retroperitoneal spaces of a girl, aged 15, with symptoms suggesting appendicitis or ureteral colic. A proliferation of cells slightly more mature than those found in typical neuroblastoma is seen.

cervical sympathetic, one in the suprarenal gland, two in the extremities, two within the skull, one in the midbrain and one on the acoustic nerve.

Three of the eight were malignant—an unusually high number. The clinical course is usually slow, marked by progressive enlargement

and eventually by symptoms of pressure. Those in the cervical region and thorax may interfere with respiration; those in the abdomen cause digestive symptoms. When occurring in the retroperitoneal spaces, the tumor may be mistaken for a malignant tumor of the kidney. Occasionally severe neuralgic pains are felt along the distribution of the nerves encroached upon. When benign, the mass is freely movable and not tender. In one case in our series the growth was extremely small.

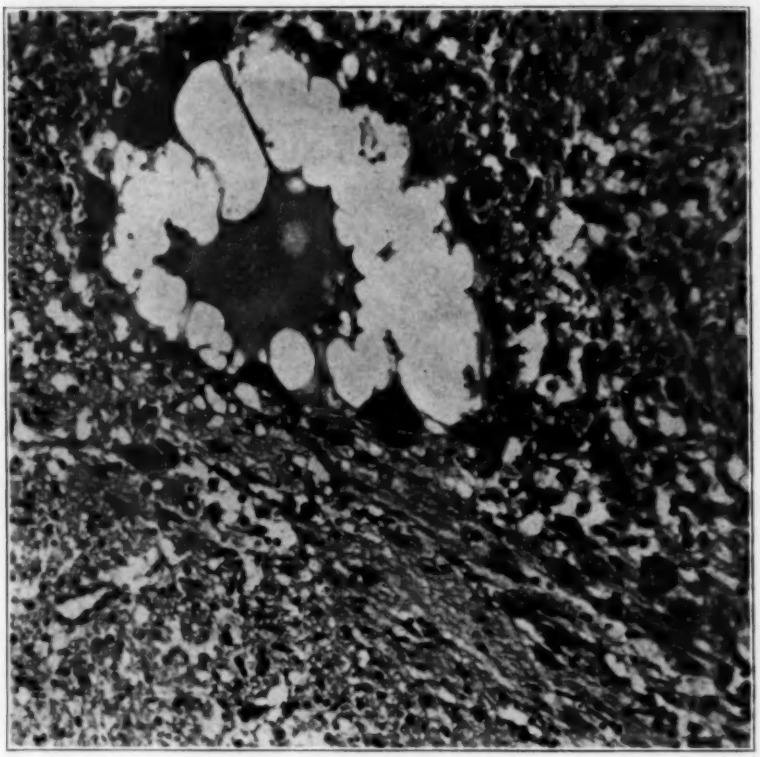

Fig. 25 (path. no. 47692).—Section from the tumor shown in figure 24. Ganglionic and adult chromaffin cells are seen embedded in a neurogenic stroma.

It developed on the auditory nerve. Because of being so rare, two of the three cases of a malignant tumor will be discussed briefly. The third case has been reported by Lewis and Hart.

A Retroperitoneal Malignant Ganglioneuroma.—A white girl, aged 15, had complained for over a year of recurrent, severe, cramplike pains in her legs. These were more severe on the right side below the knee in the muscles of the calf. Similar pains had been experienced six or seven years before. A few months before examination abdominal pain was noted. No definite diagnosis was made at that time.

When the patient was admitted to the hospital a mass could be palpated in the region of the right kidney. The right knee jerk was absent. The white blood count was 8,200, with a normal differential count. Pyelographic studies of the kidneys showed no marked deformity. The calices of the right kidney were slightly blunted, and the renal pelvis on that side seemed dilated. The right ureter was also thought to be somewhat dilated.

An operation was performed on Feb. 9, 1932. The appendix was removed through a right rectus incision and a retroperitoneal tumor palpated.

An incision was made that exposed the right kidney. A large tumor was found which extended from the right suprarenal gland, behind the ureter, down to the brim of the pelvis. The growth, which was hard and encapsulated, was removed.

Fig. 26 (path. no. 37512).—A benign ganglioneuroma arising in a cervical sympathetic in a child, aged 4, which terminated fatally. The roentgenogram shows a mass invading the mediastinum and compressing the lung.

The patient returned home on March 1. She was seen in January, 1933. At this time metastases had formed in the left parietal region. The mass was about 2 inches (5 cm.) in diameter. Her legs were atrophied. Occasional fecal incontinence was noted; amenorrhea had developed. The patient was bedridden. The tumor had the shape of an oyster. One hemorrhagic area the size of a marble was found; the remainder of the growth was firm and encapsulated. The cut surface was grayish-white with yellow flecks.

On microscopic examination two definite masses were found. In one of these stroma predominated. The stroma was formed of coarse fibers arranged in bundles, and a finer reticulated substance, which on cross-section looked like a normal nerve. In the stroma were embedded many large ganglion cells with a single nucleus, and small clumps of cells arranged in a syncytium with a cytoplasm which

stained deeply with hematoxylin. This tissue resembled somewhat normal medulla of the suprarenal gland.

The other portion of the tumor mass was very vascular and was formed of small cells, seemingly tightly packed together, with dense nuclei. The cells resembled those seen in typical neuroblastomas. Many were, however, larger with spindle or pear-shaped forms. Histologically, the tissues of the ganglioneuroma, paraganglioma and neuroblastoma were combined in this growth.

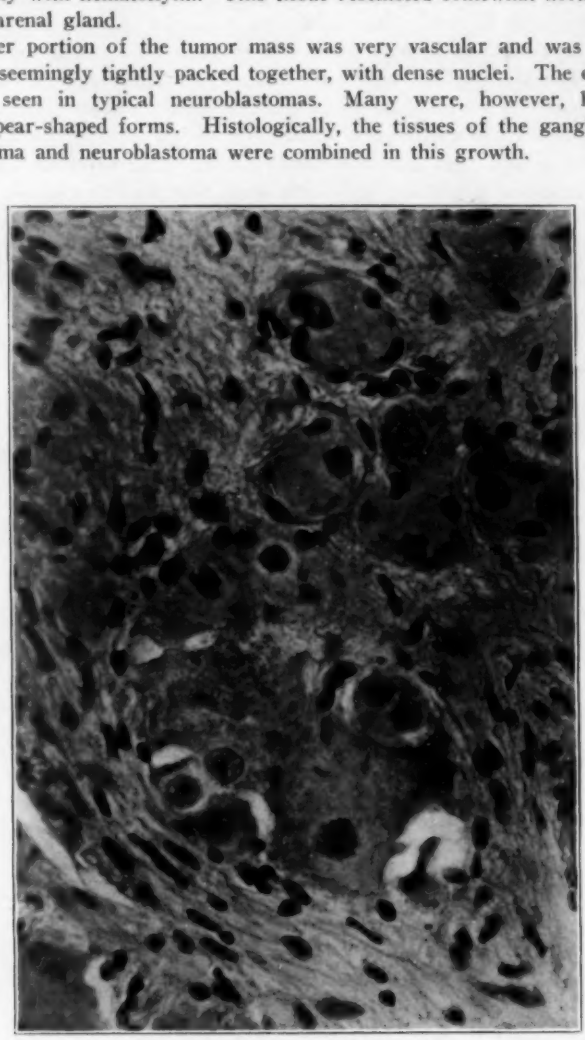

Fig. 27 (path. no. 37512).—Photomicrograph showing large ganglion cells and neurogenic stroma occurring in the tumor illustrated in figure 26.

Malignant Ganglioneuroma Occurring in the Right Popliteal Fossa.—A Negress, aged 18, had had a painful, aching sensation in the right calf for three months. When the patient was recumbent the pain was relieved. Preceding this by two years was an ailment which the patient described as a neuritis in both legs. At this time there also were noted a swelling of both legs and photophobia. The exact nature of the illness could not be determined. She attributed the pain in the right leg, complained of on admission, to a fall the year before. A definite lesion in the region of the right calf was discovered a month before.

On the posterior surface of the right thigh, about 4 cm. above the popliteal space, was a firm, tender mass which involved the soft tissues. It measured 20 by 20 by 8 cm. Its lateral and upper margins merged with and infiltrated surrounding structures. Below the popliteal space in the right calf a hard, cordlike swelling, 2 inches in length, which was extremely tender, could be palpated.

The tumor was explored on Oct. 6, 1926. It was vascular and contained mucoid tissue among the vascular areas. On October 15, the mass was excised from the thigh. The patient was admitted to another hospital in November, 1930, and an operation was performed for a recurrent tumor in the region of the right hip. The patient died on November 12, shortly after the second operation. Permission for autopsy could not be obtained.

The gross specimen measured 12 by 10 by 4 cm. It seemed encapsulated. The surface was white; the cut surface seemed fibrous, but scattered throughout were hemorrhagic and yellow areas.

The tumor varied considerably when examined microscopically. The greater portion had a hyalinized, fibrous appearance, but contained many vascular areas. In the hyalinized areas were accumulations of small spindle cells, forming a reticulum, and large spindle cells such as are found in the sarcomas arising from nerve sheaths. At the center of many such masses were cellular, fibrous areas, in which were embedded giant cells and an occasional ganglion cell. The tumor appeared to be a mixture of a benign ganglioneuroma and a sarcoma of the nerve sheath.

COMMENT

The three types of tumors which have been discussed develop from cells which wander out from the neural crest during embryonic life. The undifferentiated cell may give rise to the neuroblastoma, and as differentiation proceeds the more adult types of paraganglioma and ganglioneuroma may develop. The occurrence of all these types of tissue in the same tumor indicates a common origin, different degrees of differentiation accounting for the occurrence of the more adult type of tissue. Recently Joergensen has reported a case of hypertension associated with a retroperitoneal ganglioneuroma. Softening in the brain and spinal cord was also noted in this patient. In discussing this case he stated, "that paraganglioma has been found associated with hypertension without other discoverable etiologic factors. Some paragangliomas are composed of epinephrine-bearing tissue, while ganglioneuromas do not contain such elements." One may conclude, therefore, "that in spite of the origin of these two tumors from the common, primitive type of cell, when hypertension is associated with ganglioneuroma it is merely incidental. It is believed that the hypertension in this case can best be explained on the basis of the renal and generalized vascular changes."

No other ganglioneuromas have been reported in which hypertension was a part of the clinical picture.

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CONGENITAL CARTILAGINOUS RESTS IN THE NECK

WARREN B. MATTHEWS, M.D.
CHICAGO

Largely as a result of the historic work of Rathke [1] in 1825 on the development of structures of the head and neck from the embryonic branchial system, many hitherto unexplained anomalies of this region of the body have been better understood. Rathke noticed the similarity of the piscine gill system to the embryonic cervical structures of man, the pig, horse and chick. Other investigators followed Rathke and in rapid succession correctly related the embryonic to the normal postnatal anatomy. That congenital anomalies of the face and neck were soon interpreted as the effects of early embryonic maldevelopment is apparent. Heusinger,[2] for example, in 1864 analyzed forty-six cases of cervical and facial malformations and was well aware of their origin.

The most common defect of the branchial system in the neck of man is the lateral cervical cyst or fistula. Among the rarer defects is the presence of cartilaginous remains, or "rests," an example of which is presented in the following paragraphs.

REPORT OF A CASE

History.—A. M. B. H., a 6 year old girl, of Caucasion extraction, was brought to the clinic because of wryneck. The family history was not significant. The birth of the child had been effected by forceps delivery after a long, hard labor. She had been bottle-fed. She had always seemed healthy except for the aforementioned deformity.

When she was 3 weeks old, her mother noticed that she slept with her face turned to the left, and that a lump the size of a hen's egg was present in the right side of the neck between the right ear and the sternoclavicular junction. This lump was treated for one year by a masseuse, and during this time it gradually receded until only a very small, hard nodule remained. This persisted. The condition of wryneck seemed to the mother to have been worse during the past three years than at first.

Physical Examination.—The child was well nourished and apparently normal except for the torticollis. The left side of the head (eye, chin and ear) was held higher than the right side, and the chin pointed to the left. The right sternocleidomastoid muscle was shortened and very hard and stood out like a fibrous

From the Department of Surgery, Division of Orthopedic Surgery, University of Chicago.

1. Rathke: Isis von Oken, 1828; cited by Nieden and Asbeck.[3]

2. Heusinger: Hals-Kiemen-Fisteln von noch nicht beobachteter Form, Virchows Arch. f. path. Anat. **29**:358, 1864; **33**:177, 1865.

band. The left corresponding muscle was normal except for slight hypertrophy. Beneath the skin overlying the anterior border of the right sternocleidomastoid muscle, at a point about midway between its two ends, was a hard, movable, painless, button-like structure about 5 mm. in diameter (fig. 1). The overlying skin was normal.

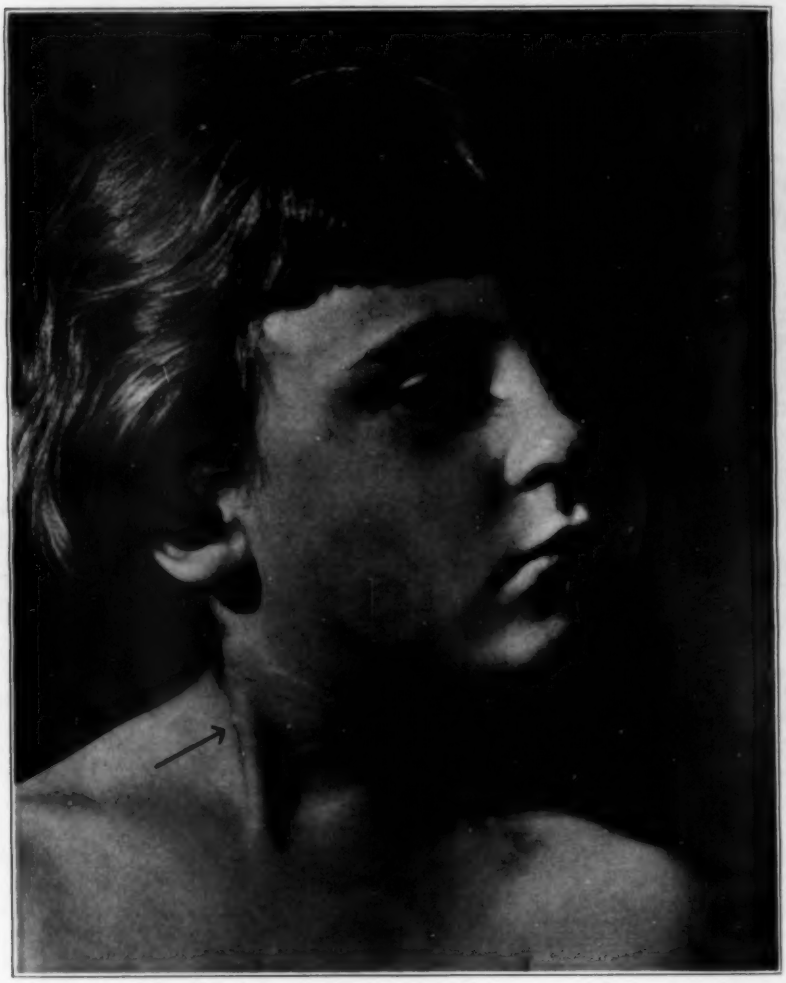

Fig. 1.—Preoperative appearance of the cartilaginous rest on the right side of the neck.

Laboratory Findings.—The results of a blood count and of urinalysis were normal. The Wassermann and Kahn tests were negative. An x-ray picture (Nov. 3, 1931) showed (1) a lack of normal development of the right half of the body of the first cervical vertebra (a congenital or an acquired defect) and (2) nonfusion of the two halves of the second thoracic vertebra with absence of its posterior spinous process.

Operations.—On Nov. 4, 1931, Dr. Edward L. Compere performed a tenotomy of the right sternocleidomastoid muscle and removed a small piece of the muscle for histologic study. It proved to be only dense fibrous tissue with no muscle fibers present.

On Nov. 30, 1931, Dr. Compere removed the button-like nodule from the right side of the neck. There were no adhesions to the underlying muscle or to any other nearby structure. Grossly, it was bluish white and of uniform, hard consistency, 5 mm. in diameter and 2 mm. thick. It had the appearance of cartilage.

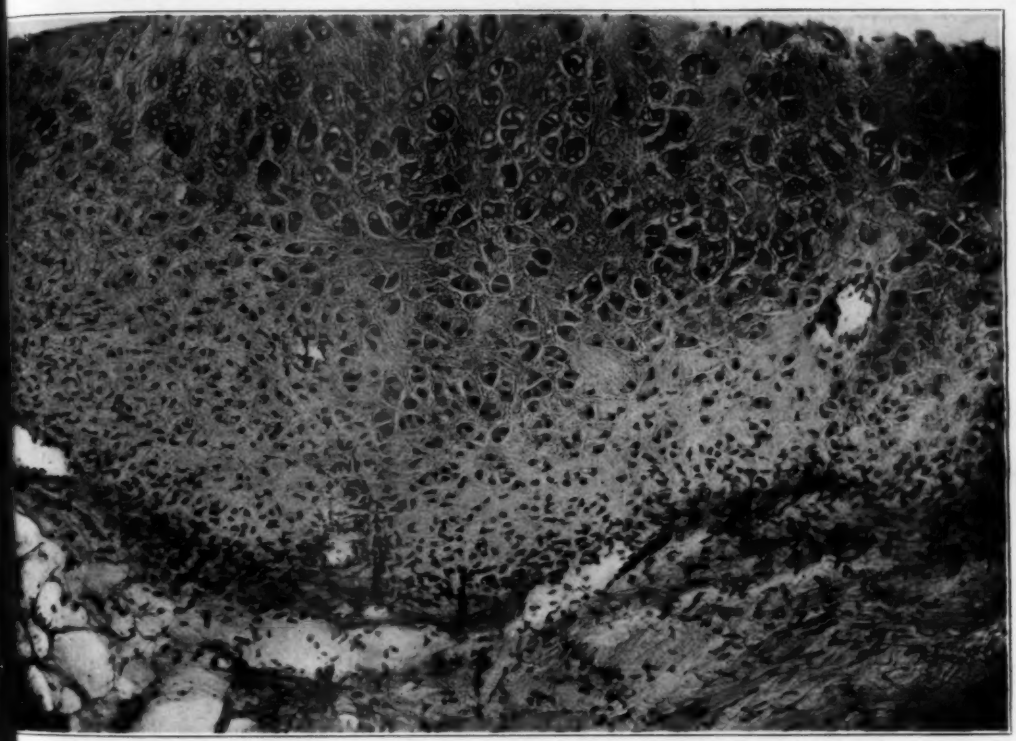

Fig. 2.—A section through one edge of the cartilaginous body; stained with hematoxylin and eosin; reduced from a magnification of × 140.

Microscopic Examination.—Sections made transversely through the specimen and stained with hematoxylin and eosin were found to be composed principally of diffusely arranged cartilage cells (fig. 2). The cell nests were irregular in outline, varying in shape from round to oval or fusiform. Most of them contained only one cell nucleus. A widely spaced intracellular portion was quite granular and seemed to have a thin framework. The more mature cells were in the more central portion of the sections, while peripherally the nuclei had more of a fibroblastic appearance. Fibrous connective tissue surrounded the cartilage and in at least one area invaded it as though through an indentation.

From the foregoing study the diagnosis of hyaline cartilage was made. However, after a search was made for elastin by Dr. P. A. Delaney of the depart-

ment of pathology (by staining with phosphotungstic acid and hematoxylin), the diagnosis was of necessity changed to elastic cartilage. In the hyaline matrix surrounding the lacunae were found many branching fibrils of elastin, interlacing like so many pieces of straw (fig. 3).

The question might be raised as to whether or not this cartilage developed as a result of the birth injury that apparently had caused a large hematoma in the right sternocleidomastoid muscle and led finally to its fibrous degeneration. Because of the nature of the cartilage, and

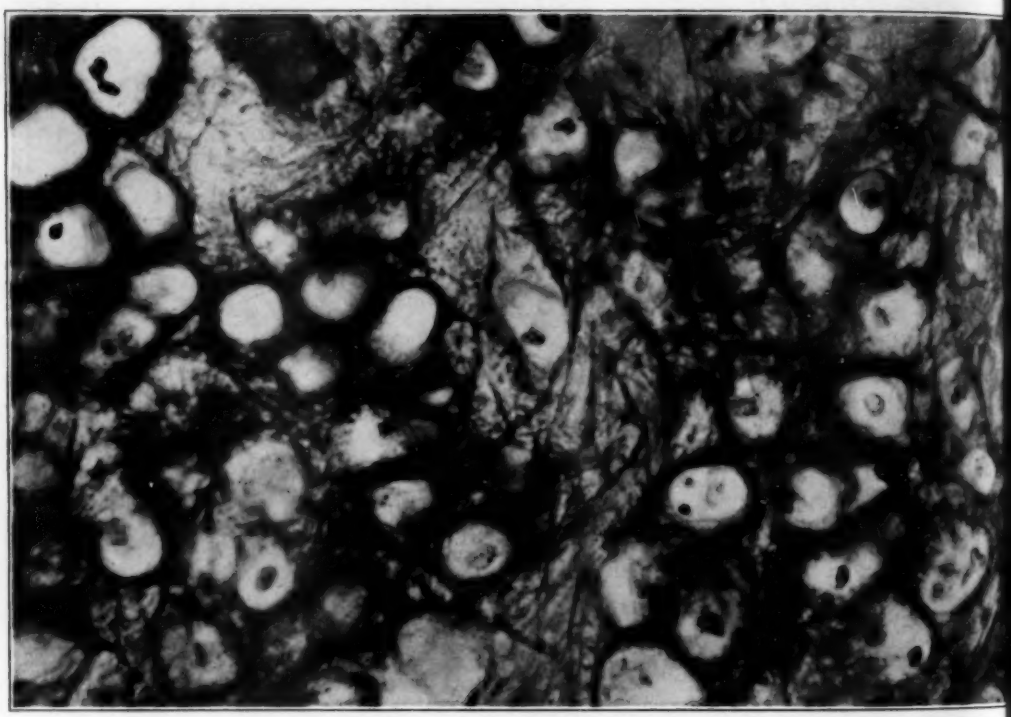

Fig. 3.—A section of the cartilage stained with phosphotungstic acid and hematoxylin; reduced from a magnification of × 700. Sections stained by Weigert's method presented the same picture. The fibers of elastin are clearly visible.

because it was completely detached from the underlying scarred muscle, I feel that this was not the case. This cartilage was much more probably a congenital remnant from the embryonic branchial system.

Of additional interest is the occurrence of the anomalous malformation of the second thoracic vertebra, which is in accordance with the common observation that maldevelopment of the branchial system is often associated with other congenital defects.

INCIDENCE

The first two cases reported were described by Heusinger [2] in 1864. Since that time reports of between seventy and eighty cases have appeared in the literature, according to a careful recent review made by Nieden and Asbeck [3] (1931). Because in several cases among this number operation was not performed or tissue removed surgically was not adequately studied histologically, the precise number is inexact. It is certain, however, that this finding is very infrequent. By far the majority of instances have been reported by European writers, and very few by American authors. Nieden and Asbeck believe that cartilaginous growths in the neck were observed by the early Greeks—that it must have been such observations that led Greek sculptors to adorn images of satyrs with horns arising just beneath the ears.

PATHOLOGIC ANATOMY

These symptomless cartilaginous tumors have been found at a typical site: between the hyoid bone, above, and the sternoclavicular junction, below; they always lie over the sternocleidomastoid muscle, usually near its anterior edge. In general, they have been found in the same locations as those where lateral cervical fistulas commonly open.

In size, these tumors vary widely between nodules the size of a millet seed and those the size of a pigeon's egg. In some instances, the nodule, if large, has hung down in a pedunculated pouch of skin. There is no typical shape; some are button-like or coinlike, and others are roughly cylindric or oval. A diagnostic feature is their hard consistency. They are not attached to the overlying normal skin and seldom to the underlying muscle, though nearly always rather firmly united with the superficial fascia of the neck. Blood vessels and nerves have been found in association with these pieces of cartilage. No mention has ever been made suggesting their attachment to thyroid or hyoid cartilage. In a fair number of the cases reported the cartilage has been found symmetrically bilateral. A few of the cartilage bodies were found in the walls of lateral cervical fistulas.

In all of the reports, save one which described elastic cartilage, the tissue was stated to be fibrocartilage. Many of the reports were made before the current distinction between elastic and fibrocartilage was so universally adopted. Perhaps some of these cases might now be classified as instances of elastic cartilage. The one case of elastic cartilage was described by Nieden and Asbeck, who made several hundred serial

3. Nieden, H., and Asbeck, C.: Kongenitale Knorpelreste am Halse und ihre Beziehung zu den seitlichen Halsfisteln, Beitr. z. klin. Chir. **153**:47, 1931 (literature).

sections and a wax model of their specimen. By this detailed examination they demonstrated two epithelial inclusions in the form of small cysts between the cartilaginous bars—supposedly pinched-off portions of branchial clefts.

There is in the literature no suggestion of malignant changes in these cartilaginous remnants.

PATHOGENESIS

In all the reports the authors have assumed that the cartilage originated as an isolated segment of a branchial arch. In this belief they have followed the teachings of the embryologists who interpret lateral cervical fistulas as being due to the persistence of branchial clefts. A great deal of discussion has taken place as to which one of the branchial clefts remains as a lateral cervical fistula, and which arch persists as an anomalous piece of cartilage. Nieden and Asbeck suggest that one might settle the question by following up the nerve supply to the fistula or cartilaginous body, since the derivatives of each arch and cleft have constant and characteristic innervations.

Hyaline cartilage occurs in the adult in the nose, larynx, trachea and bronchi. Elastic cartilage is found in the external ear, in the walls of the external auditory canal and eustachian tube, in the epiglottis, and in the corniculate and cuneiform cartilages. To the construction of these parts all the first five branchial arches contribute. Fibrocartilage forms the interarticular cartilages of the lower jaws.

Wenglowski,[4] in 1907, challenged the branchial origin of lateral cervical fistulas and pouches and of any associated anomalous structure. This author spent most of his time for several years collecting from numerous obstetric and gynecologic services throughout Russia seventy-eight human embryos, measuring from 2 to 49 mm. Five years were spent in making serial sections and wax models of these specimens. In addition, he carefully studied many cases of cervical cyst and fistula in children and adults. As one of the conclusions of this laborious and conscientious work he postulated that cysts and sinuses occurring along the mesial border of the sternocleidomastoid muscle, ranging from the hyoid bone to the suprasternal notch, are vestigial remains of the thymicopharyngeal duct. No embryonic remnant appearing in the neck below the hyoid bone can originate from the branchial system, according to Wenglowski. His work is discussed in some detail in a recent paper by H. W. Meyer[5] (1932). Many lateral cervical fistulas which

4. Wenglowski, R.: Ueber die Halsfisteln und Cysten, Arch. f. klin. Chir. **100**:789, 1913.

5. Meyer, H. W.: Congenital Cysts and Fistulae of the Neck, Ann. Surg. **95**: 1 and 226, 1932.

are patent throughout, and which open externally at the site just indicated, follow just the course taken by the thymic canal. This canal originates from the third pharyngeal pouch.

Wenglowski did not specifically mention cartilaginous remains in his discussion, nor is there an example included in the list of anomalies that he collected. Because these cartilaginous remains sometimes exist in the walls of, or in relation to, lateral cervical fistulas or cysts, one naturally supposes that these structures have a common origin. Therefore, one must conclude either that all the authors who have reported cases of cartilaginous remains in the neck have been in error when they have attributed them to a branchial origin or that these bodies have no embryonic connection with the lateral cervical fistulas with which they may be so intimately related.

SUMMARY

1. An instance is described in which a particle of elastic cartilage was found in the side of the neck of a 6 year old child. I think that this cartilage originated as a remnant of a branchial arch.

2. A brief review of the incidence, pathologic anatomy and pathogenesis of cartilaginous rests in the neck, as described in the literature, is presented.

EWING'S TUMOR (PRIMARY INTRACORTICAL AND SUBPERIOSTEAL LYMPHANGIO-ENDOTHELIOMA)

REPORT OF A CASE

DOMINIC A. DE SANTO, M.D.
Assistant Pathologist, Bellevue Hospital
Instructor in the Department of Medicine, College of Physicians and Surgeons
NEW YORK

Whoever studies the subject of endothelioma of the bones and endothelial tumors in general cannot fail to be struck by the great confusion in terminology and classification which exists in this field. Unfortunately, the group of the endotheliomas has become a conglomerate composed of many tumors of unusual appearance and histology. Since the morphology of endothelial tumors is, in general, far less distinctive than is that of epithelial tumors, it is not unnatural that the pathologist confronted with microscopic sections of an unusual tumor which resembles neither carcinoma nor sarcoma should choose the middle ground and make a diagnosis of endothelioma.

Although Ewing [1] was not the first to describe endothelial tumors of bone, he was the first to present a large series of cases, and, what is even more important, it was he who separated these growths into a fairly distinct clinical and roentgenologic group. Previously, the literature on the subject had consisted of reports of a heterogeny of diversified tumors some of which were undoubtedly metastatic, since few of the studies were based on autopsy. Not unlikely, a great deal of misinformation crept into the literature which still is misleading. For example, the conclusion of Howard and Crile,[2] who reviewed the literature up to 1902 and found that endotheliomas occurred in persons whose ages averaged 60 years (except in the three cases in their own series), is at great variance with that of Geschickter and Copeland,[3] who found that 95 per cent of a series of 65 endotheliomas occurred in persons

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From the Department of Pathology, Bellevue Hospital.
Reported with the permission of Dr. Carl Burdick, Director, Fourth Surgical Division.

1. Ewing, James: (*a*) Diffuse Endothelioma of Bone, Proc. New York Path. Soc. **21**:17, 1921; (*b*) Further Report on Endothelial Myeloma of Bone, ibid. **24**:19, 1924.

2. Howard, W. T., and Crile, G. W.: A Contribution to the Knowledge of Endothelioma and Perithelioma of Bone, Ann. Surg. **42**:358, 1905.

3. Geschickter, C. F., and Copeland, M. M.: (*a*) Tumors of Bone, New York, American Journal of Cancer, 1931, p. 379; (*b*) Ewing's Sarcoma: Small Round Cell Sarcoma of Bone, Arch. Surg. **20**:246 (July) 1930.

under 25. Obviously, the older cases represented a condition different from the present conception of Ewing's tumor—probably metastases to the bones.

The disease named after Ewing [1a] was reported by him in 1921 as an example of bone tumor occurring in the distal end of the radius of a girl aged 14. Its histologic and gross appearance differed so markedly from that of the usual osteogenic sarcomas that he felt the necessity of a separate grouping. Subsequently, Ewing [1b] collected seven instances of this tumor and summarized his findings about as follows:

1. The tumor occurs in young persons from 14 to 19 years of age.

2. The bones affected are the tibia, ulna, ischium, parietal bones and scapula.

3. The tumors grow slowly, several months usually elapsing before they attract attention. They are often painful and tender.

4. The roentgenogram is characteristic: A large portion or the whole of the shaft is involved, and the ends are usually spared. Unlike osteogenic sarcoma, the tumor produces slight widening of the shaft, but with a gradual fading of osseous structure and absence of production of bone.

5. The tumors are radiosensitive. This is probably the most important single reason for their separate grouping.

Since the original descriptions, numerous large series of cases have been reported, notably those of Connor,[4] of Kolodny,[5] who studied the material of the Bone Sarcoma Registry, and of Geschickter and Copeland.[3] The results of the latter two studies differ from the conclusions of Ewing, which were supported by Connor, in at least one important conclusion, namely that *absence of production of bone is not a characteristic feature*. Many of their specimens showed production of bone to be as abundant as that encountered in osteogenic sarcoma, and this was true in the case to be reported. Indeed the majority showed osseous formation either parallel to or at right angles to the shaft. To regard Ewing's tumor as a primary osteolytic tumor of the medullary cavity, as is often done, is erroneous and has been responsible for many mistakes in roentgenologic diagnosis.

As an example, a recent paper reports the case of a 62 year old man with rapidly developing cachexia and a tumor involving the upper end of the humerus, the glenoid fossa and the entire scapula. Pathologic fracture of the humerus occurred. The roentgenogram of the humerus showed marked destruction of bone at the anatomic neck. The cortex was expanded. The glenoid presented a moth-eaten appearance. Shortly before death hematuria developed. The patient died of a traumatic fracture of the femur. Areas of the tumor were characterized by a

4. Connor, C. L.: Endothelial Myeloma, Ewing, Arch. Surg. **12**:789 (April) 1926.

5. Kolodny, A.: Bone Sarcoma, Surg., Gynec. & Obst. **44**:126, 1927.

solid growth of tumor cells of irregular size and shape, many being gigantic forms with vesicular nuclei and prominent nucleoli. This case, in which the diagnosis was probably made on roentgenologic findings, violates every clinical and pathologic criterion of Ewing's tumor; namely, the age of the patient; the location, with involvement of the cavity of the joint; the occurrence of pathologic fracture; the rapid cachexia, and the histologic appearance of irregularity in the size and shape of the cells.

Again, some of the published reports in the French literature, in which a great deal is being written about Ewing's tumor, describe rarefying tumors of the medullary cavity and show photomicrographs of large clear polyhedral cell tumors indistinguishable from hypernephroma. The diagnosis of Ewing's tumor is apparently being made when it is not justified. It is a rare disease comprising from 7.5 per cent to 15 per cent of all tumors of the bones. Hence, it falls to the lot of few surgeons and pathologists to see more than an occasional case in a lifetime.

NATURE OF EWING'S TUMOR

The uncertainty which surrounds the origin and nature of Ewing's tumor is expressed by the great variety of names by which it is known. "Diffuse endothelioma," "endotheliomyeloma" (Ewing), "Ewing's sarcoma" and "reticular sarcoma of the bone marrow" are but a few. Even the primary site of its appearance is a subject for controversy. Connor [4] placed it in the marrow cavity, and Ewing [1b] himself once leaned to this view. Kolodny [5] believes in an origin from multicentric foci in the medulla and cortex which soon coalesce. Geschickter and Copeland,[3] whose studies are more recent and supported by more roentgenologic evidence, believe in a primary subperiosteal or intracortical origin with secondary and minimal medullary invasion. This is in strict though not absolute contradiction to the original views of Ewing,[1b] who chose the name endotheliomyeloma in order to indicate either a medullary origin or a preponderance of medullary involvement. The pendulum appears to have swung to the opposite extreme.

The following case is reported because it is undoubtedly an example of Ewing's tumor and appears to establish the origin of the disease.

REPORT OF CASE

History.—J. V., a Puerto Rican boy, aged 5 years, had been a normal infant born at full term. The family history showed no evidence of syphilis. He had had the usual diseases of childhood, measles, diphtheria and chickenpox during his fourth year, and tonsillectomy had been performed seven months before his admission to the hospital. Eight months before his admission, the left leg began to swell and caused pain when he walked. At that time he entered another institution

where he remained for a short time. Roentgenologic studies were made, and the diagnosis was osteomyelitis. The family refused to permit operation and withdrew the child from the hospital. He was admitted to the children's surgical service at Bellevue Hospital on Jan. 21, 1932.

Physical Examination.—The patient was slightly undernourished. The left tibia showed a smooth, diffuse, spindle-shaped enlargement of the entire shaft, which stretched the overlying skin. The leg was not tender, and the overlying soft tissues did not appear inflamed.

The submaxillary, tonsillar, inguinal and cervical nodes were slightly enlarged. Physical examination otherwise gave negative results. No stigmas of syphilis or rickets were present.

Fig. 1.—*A*, photograph of the specimen. The arrow indicates a hemorrhagic cyst. *B*, roentgenogram taken in August, 1931, shortly after the onset of pain. There are periosteal elevation on the lateral surface of the tibia and new bone formation. Note also the increased density of the lateral half of the proximal portion of the tibia, indicative of new bone formation in the medulla. The roentgenologic diagnosis was chronic osteomyelitis. (Reduced from an 8 by 10 inch film.) *C*, roentgenogram taken on Feb. 15, 1932, showing extensive formation of bone beneath the periosteum and at right angles to the shaft, and also increased density of the medullary cavity. The epiphysis is uninvolved. The diagnosis was osteogenic sarcoma. (Reduced from a 12 by 14 inch film.)

Laboratory Findings.—Roentgenograms of the long bones and of the lungs were made. The roentgenogram of the left tibia showed separation of the periosteum with evidence of formation of new bone springing radially in both directions. The upper end of the shaft showed several areas of osseous rarefaction. The lungs,

the bony thorax and the long bones contained no metastatic foci. Several roentgenograms were taken without leading to a substantial change in the diagnosis, which was "osteogenic sarcoma." This diagnosis was made despite the failure of the tumor to involve the epiphyses and was based on the predominance of production of bone.

The original roentgenograms taken eight months before the patient's admission were consulted. These showed the periosteum of the upper third of the left tibia to be raised on both the inner and the outer aspects. There was production of new bone beneath the raised periosteum at right angles to the long axis of the bone together with irregular production of bone in the upper end of the shaft. The process in no instance extended beyond the epiphyseal line.

Course.—The patient received radiation therapy on January 27. Biopsy was performed on February 5. Following the report on the biopsy, amputation of the

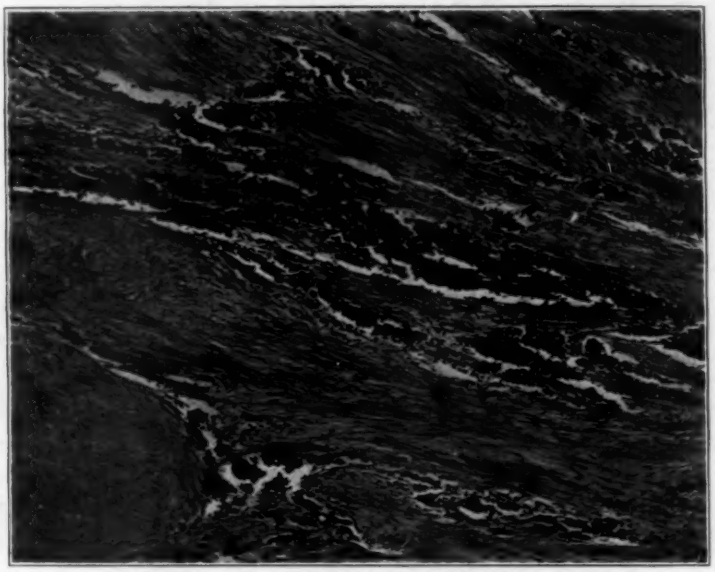

Fig. 2.—Photomicrograph of the periosteum showing invasion by a tumor which extends along slitlike lymphatic spaces. Hematoxylin-eosin stain; × 100.

middle part of the thigh was performed on February 15 by Dr. Beekman and was followed by a course of erysipelas and prodigiosus toxins (Coley) administered with slight interruptions until the date of discharge, which was May 15, 1932.

The patient is alive and well at the time of writing, with no clinical or roentgenologic evidence of metastases.

Gross Pathologic Study.—The description is concerned with the tibia alone. The specimen was 23 cm. in length and 5 cm. in maximum width, which was at the midshaft. The periosteum of both the inner and the outer surfaces was raised from the cortex for an average distance of 1 cm. Beneath the periosteum was a fairly dense deposition of bone arranged at right angles to both the periosteum and the shaft. The new bone varied considerably in consistency, being dense in some places and soft and spongy in others. The process stopped sharply at the proximal epiphysis and ended distally about 5 cm. from the lower epiphyseal junc-

tion. In the middle of the shaft on the inner aspect directly in the region of subperiosteal formation of new bone was located a cyst, approximately 2 by 1 cm. in size, which was bridged by slender strands and filled with chocolate-colored material.

The cortical bone was lamellated, and instead of having a compact structure it was composed of a series of parallel, splinter-like units of bone. In the midshaft, the cortex was widened, encroaching on the marrow cavity. The medullary cavity of the entire shaft was composed of spongy bone of varying degrees of density, and only in the uninvolved distal portion was there any marrow. In general, the dense bone was at the proximal end of the shaft. The epiphysis and the epiphyseal line appeared natural.

Microscopic Examination.—Sections were removed in the following manner: (1) a transverse block of bone from periosteum to periosteum including the cortical

Fig. 3.—Photomicrograph of the cortical bone. The lamellae are separated, and the haversian canals are widened. Note the dilated perivascular lymphatics whence the neoplasm presumably arises. Hematoxylin-eosin stain; × 100.

bone; (2) a transverse block of bone from periosteum to periosteum not including the cortical bone; (3) a block of bone through the proximal epiphyseal junction, and (4) a block of bone through the cystic area.

These were fixed in 10 per cent formaldehyde, decalcified in 10 per cent nitric acid, embedded in paraffin and stained by routine methods. In addition, the Giemsa and van Gieson stains and a Pianese stain for colloid were used.

In the microscopic report, for convenience of description the four zones in the tumor will be considered: (1) the periosteum and surrounding muscular tissues; (2) the subperiosteal zone of new bone formation; (3) the cortical bone, and (4) the medullary cavity.

Because of technical difficulties incident to the cutting of sections of bone, most microscopic studies are based on examination of small pieces of tissue, often dis-

closing an atypical histologic picture. In this case an attempt was made to study the topography as well as the histology of the tumor.

Periosteum: The periosteum was studied by means of transverse and tangential sections. It appeared as a slender band of dense collagen fibers, surrounded in areas by striated muscle. The periosteum at the proximal end of the shaft appeared thickened and was occupied by a growth presenting the following characteristics: The cell was approximately the size of a lymphocyte with a round nucleus containing scattered chromatin particles. The nucleus was characteristically round but in rare instances vesicular and elongated. The cytoplasm was clear; it was usually indistinct, but when visible was polyhedral. The cells were uniform in size and shape. In the periosteum the cells were arranged in compact masses, strands and branching columns and invariably were found lying in slitlike tissue spaces lined by endothelium.

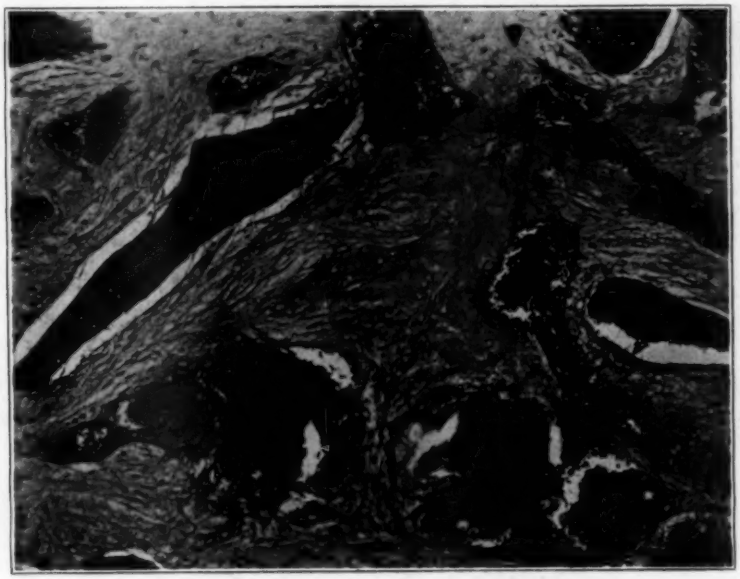

Fig. 4.—Photomicrograph through a block of subperiosteal tissue. Note the dilated perivascular lymphatics, the laying down of new connective tissue and the spicules of newly formed bone. Hematoxylin-eosin stain; × 100.

Subperiosteal Zone: In this zone two separate processes were present, one of formation of bone, and the other of tumorous infiltration. The zone was occupied by a meshwork of osteophytes, usually arranged at right angles to the long axis of the bone. These osteophytes represented new spicules of bone and could be seen in every stage of formation by the agglomeration of osteoblasts. Occasionally chondroblasts with acidophilic nuclei formed a peripheral zone in the spicule.

The osteophytes were embedded in a stroma of vascular loose fibrous tissue. Large distended blood vessels were present in this stroma lying in the same direction as the newly formed bony trabeculae.

The tumor was represented by a structure consisting of a multitude of elongated, vesicular spaces lined by several rows of cells identical with the tumor cells described and containing compact masses of the cells lying free in the lumens.

The spaces appeared to intercommunicate freely, giving the whole a loose reticular aspect. As the tumor was traced inward and toward the cortex it assumed a more cystic character and was composed chiefly of a multitude of oval spaces lined by a single or a double row of tumor cells and containing fluid that had unquestionably the staining properties of lymph. There was a diffuse growth of small tumor cells, but the cystic nature of the growth predominated. The dilated lymph spaces (which they undoubtedly were) often lay adjacent to osteophytes but were in no way directly transformed into osseous tissue. Often, papillary infoldings lined by endothelium could be seen projecting into them. Often the coalescence of numerous such spaces produced a multilocular cyst.

Fig. 5.—Higher magnification of dilated subperiosteal lymphatics. Note the lining endothelium, the papillary ingrowth of endothelial cells and the fluid lymph. Hematoxylin-eosin stain; × 500.

Elsewhere the lymphatic spaces were seen to contain red blood cells, and in a few instances it was possible to find capillaries which appeared to have ruptured into them.

The hemorrhagic cyst represented a multilocular endothelial space full of red blood cells. Several smaller ones were found.

Cortical Bone: The cortical bone appeared as a series of parallel layers of vertical spicules, widely separated by an overgrowth of connective tissue in the haversian canals. The capillaries were greatly distended and were surrounded by numerous dilated lymph spaces presenting a picture of lymphatic obstruction with

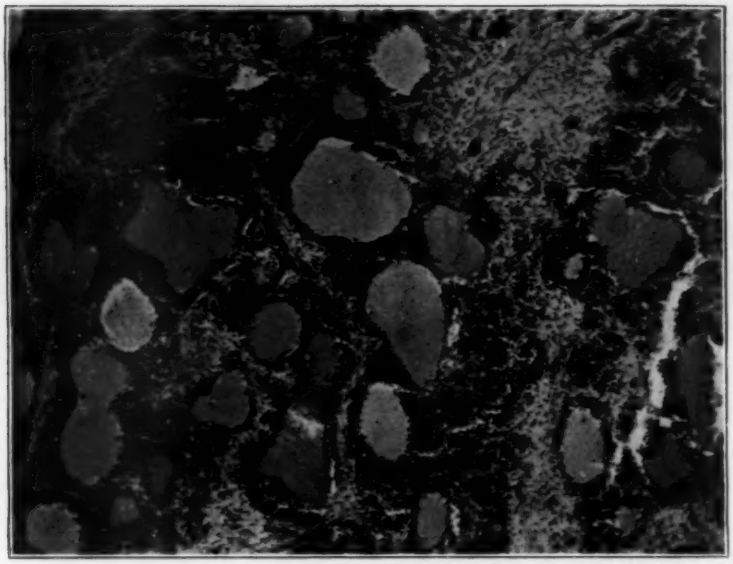

Fig. 6.—Photomicrograph of an area in the medullary cavity. The tumor is composed of many spaces full of lymph and surrounded by several rows of small, round cells. Hematoxylin-eosin stain; × 100.

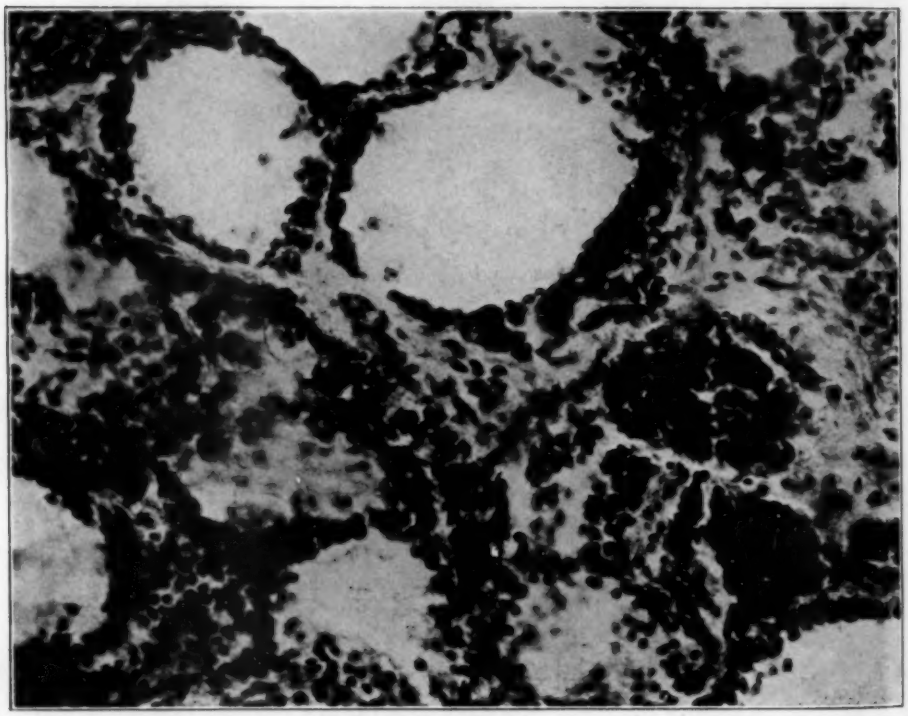

Fig. 7.—A higher magnification of the section shown in figure 6. Hematoxylin-eosin stain; × 500.

dilatation rather than one of autonomous new growth of lymph channels. The perivascular relationship of lymph spaces to capillaries and venules was constantly maintained.

Old osteophytes were seen to undergo resorption, but production of new bone was also conspicuous. The resorption did not appear to depend on osteoclastic activity, for osteoclasts were seldom observed.

Marrow Cavity: The medullary cavity was occupied by a diffuse overgrowth of fibrous connective tissue throughout which were scattered interlacing spicules of bone, dilated blood spaces and perivascular lymph channels. In general the structure was like that of the subperiosteal zone except that the growth was comprised chiefly of multicystic lymph spaces and showed less diffuse cellular overgrowth. No fatty or hematopoietic elements were present.

Summary of Microscopic Observations: The histologic picture was that of a tumor both angioblastic and osteogenic in its tendencies. The production of bone was not derived from the tumor-forming elements; rather the formation of new lymph spaces would appear to favor the theory of a nutritional stimulation to osteogenesis.

The angiomatous elements appear in their most natural state in the cortical bone as dilated perivascular lymphatics, whence they may be traced inward to the medullary cavity and outward to the zone of subperiosteal ossification; in either location the growth assumes a neoplastic character of tissue spaces lined by endothelial tumor cells, containing tumor cells and lymph in their lumens and surrounded by a diffuse growth of tumor cells. In the periosteum the growth is diffuse along tissue spaces and seems restricted to the periosteum overlying the proximal end of the shaft.

NOTE.—In December, 1932, approximately ten months after the amputation, metastases developed which involved both angles of the mandible, the occiput of the skull and the forehead in the midline at the root of the nose. The patient was readmitted to the hospital. There was no roentgenologic evidence of metastases to the lungs or to the other long bones.

The case was registered with the Bone Sarcoma Registry and was diagnosed as "Ewing's sarcoma."

The patient died on July 26, 1933, at the age of 6½ years. Autopsy was performed on July 27, 1933.

Autopsy.—The anatomic diagnosis was: Ewing's tumor (lymphangio-endothelioma), primary, in the left tibia with metastases to the skull, vertebrae, iliac bones, right femur, ribs, left lung, pericardium and diaphragm.

The body was that of a small boy, 6½ years of age, 3 feet and 2 inches (96.44 cm.) in length; the estimated weight was about 35 pounds (15.9 Kg.). The skin was light brown, that of a negroid type of Puerto Rico. The features, likewise, had a negroid appearance. The left lower extremity had been amputated at the midthigh, leaving a small stump, 3 inches (7.6 cm.) in length, completely closed by skin and soft tissue. The head had a grotesque appearance. It possessed, more or less, the shape of a parallelogram, the longer diagonal, from the vertex to the chin, measuring 12 inches (30.48 cm.), and the shorter diagonal, from the occiput to the forehead, measuring 9 inches (22.86 cm.). This peculiar shape resulted, in part, from a large tumor covering the occipital regions of the skull, measuring 7 by 3 by 2 inches (17.78 by 7.6 by 5 cm.). A smaller metastasis, 1½ inches (3.77 cm.) in diameter, overlay the right parietal area. Both growths were firm but not hard. The forehead was covered by a metastatic tumor, which extended in a horizontal direction from the middle of the right supra-orbital base

to the outermost border of the left supra-orbital base. It was 4 inches (10.16 cm.) long and raised about 1 inch (2.5 cm.).

Both eyes were almost completely everted from their sockets. The angle of the right mandible was enlarged by a spherical mass, 1½ inches (3.77 cm.) in diameter, firm and bony. The entire left ramus of the mandible was involved in a huge globular swelling, which extended to include the left submaxillary area and the left maxilla. This mass was, roughly, about 5 inches (13 cm.) in diameter. The skin overlying it was green and discolored.

There was a small opening, about 2 inches (5 cm.) in front of the lobule of the left ear, from which exuded some foul-smelling pus. The oral cavity was almost completely filled with a bulging tumor, covered by mucosa, which was undoubtedly continuous with the growth in the left mandible and maxilla. The teeth were distorted and irregular; many were loose and could be withdrawn from their sockets. No lymph nodes were palpable in the cervical, supraclavicular, axillary or inguinal regions.

The chest, externally, showed some small metastases to the ribs, one involving the right sixth and seventh ribs in the anterior axillary line, another involving the left ninth rib.

In the upper third of the right femur there was palpable a nodular, firm swelling, undoubtedly a metastasis.

The body was extremely wasted. On section, there was no subcutaneous fat. The muscles appeared wasted. When the abdominal cavity was opened, the peritoneum was smooth and shiny. The liver seemed slightly enlarged and low, extending about 1 inch (2 cm.) below the costal margin.

An exploration of the abdomen revealed a retroperitoneal tumor overlying the body of the second lumbar vertebra in, and to the left, of the midline, and a second mass filling the left iliac fossa. The diaphragm was at the fifth rib on the right and at the fifth space on the left, in the anterior axillary line. The right dome was inverted by a globular mass, undoubtedly occupying the thoracic cavity.

Chest: When the soft tissue of the chest was reflected, the metastases to the ribs on the right and left were seen to lie precisely at the respective costochondral junctions. The metastasis on the right was approximately spherical, 2½ inches in diameter; it extended into the right pleural cavity and was attached to the lower lobe of the right lung. This was the mass which depressed the diaphragm.

Heart: The heart weighed 100 Gm. Epicardial fat was absent. A small mass, ¼ inch (0.6 cm.) in diameter was attached to the outer surface of the parietal pericardium, posteriorly. The pericardial cavity contained about 25 cc. of clear fluid. The heart was otherwise normal.

Lungs: The right pleural cavity contained 25 cc. of fluid. The left contained about 50 cc. The lungs weighed 360 Gm. They were markedly edematous. The left lung contained a metastasis in the lower lobe, ½ inch (0.77 cm.) in diameter, directly beneath the pleura. This was soft on section and bulged from the cut surface.

Liver: On the superior posterior aspect of the right lobe, there was a minute metastasis, ¼ inch (0.6 cm.) in diameter. The liver otherwise was normal.

The spleen, kidneys, suprarenals, pancreas, gastro-intestinal tract, bladder and testes were essentially normal.

Bones: The vertebral column showed a slight curvature with the convexity to the right. On section through the vertebrae, the marrow was bright red.

Metastases which had a contrasting yellow color were found occupying the bodies of the lower sixth dorsal and the second, third and fourth lumbar vertebrae. These were usually distinctly central in position and did not involve the intervertebral disks. The metastasis in the second lumbar vertebra was continuous with a mass 2 inches (5 cm.) in diameter, already described, which overlay the anterior aspect of the body retroperitoneally.

Iliac Bones: The left iliac bone contained a tumor that completely filled the fossa, measuring 4 by 3 inches (10.16 by 7.6 cm.). This mass invaded the bone and cartilage of the iliac crest. It was relatively soft and could be excised with a knife. It was yellow and somewhat gritty on section. The left ilium contained a smaller metastasis in the fossa, roughly 1 inch (2.5 cm.) in diameter.

Femur: An incision was made over the medial aspect of the right femur disclosing a metastasis, about 1 inch (2 cm.) in diameter, occupying the cortex and medulla of the bone, at the level of the upper third.

Head: When the scalp was reflected virtually both the parietal bone and the occipital bone were replaced by grayish-white, soft tumor tissue. The occipital mass already measured and described was the largest, but the tumor replaced virtually the entire parietal and occipital areas from left to right. These metastases could be excised from the skull. They were grayish white, soft and extremely moist on section, but contained yellowish, fatty areas, presumably degenerated, and were streaked with gritty deposits of bone. The occipital bone was considerably thickened and measured ½ inch (1.77 cm.) in thickness. The temporal bones were 1/16 inch (0.15 cm.) and the frontal bone was ⅛ inch (0.3 cm.) in thickness. The inner surface of the skull was unevenly eroded and ulcerated and also showed flat elevations of tumor growth. The outer surface of the dura was extensively covered with metastases. The inner surface was smooth and not involved. Tumor tissue replaced the crista galli in the midline and extended into both orbital fossae. In these sites, the tumor was almost gelatinous.

The brain weighed 1,050 Gm. and was pale and soft, but otherwise was not unusual.

Microscopic Examination: Examination of the various metastases showed tumor tissue composed of small, round cells, approximately the size of lymphocytes. Each cell possessed an oval nucleus which was richly chromatic, a solitary nucleolus and a scattering network of chromatin. The cytoplasm was rarely visible. There was marked uniformity in the size and shape of the tumor cells. There were large numbers of mitotic figures.

In the metastases, the growth was diffuse and exhibited none of the angioblastic tendencies of the primary tumor. There was a delicate supporting reticulum. Many areas showed widespread necrosis.

No metastases were found in the deep iliac lymph nodes. The cells were identical in appearance with those in the primary growth.

COMMENT

So many cases of Ewing's tumor are on record that the mere addition of another case would serve little purpose. I feel, however, that the case reported is unique in that the histologic picture was such as to permit tracing the tumor to its site of origin. I feel, too, that there is a great deal of contradiction between the old and the more recent discussions of this subject, and that an exposition of these differences may serve to clarify the understanding of the disease.

There can be little doubt that the growth is an example of Ewing's tumor. The age of the patient, the clinical history and the characteristic error in diagnosis (osteomyelitis), the gross characteristics, particularly the limitation to the shaft without involvement of the epiphysis, and the invasion of the haversian systems and of the marrow cavity, with reactive formation of bone and fibrosis, all seem typical. The old idea of an osteolytic tumor located in the midshaft of a long bone should undoubtedly be abandoned.

I am aware of the dangers of attempting to trace the origin of a tumor on histologic grounds alone. In no field is the opportunity for error so great as in that of endothelial tumors, the characteristics of which, lying intermediary between those of epithelial and those of mesoblastic tumors, render confusion in either direction most likely. Yet there can be no doubt that the tumor originates spontaneously from the endothelium of lymph vessels since a direct continuity is established between seemingly normal though dilated lymph spaces in the haversian canals and the abnormal ones in the subperiosteal and medullary zones. Moreover, proliferating endothelium, multiple layers of endothelium and sprouts of endothelium growing out into connective tissue were frequently observed. Further, the tumor maintains its angioblastic arrangement throughout and produces a secretion of lymph fluid.

Although the structure of Ewing's tumor is described in most cases as diffuse, exceptions to this are frequent. Endothelial tumors are classified by Ewing [6] as: (1) interfascicular (consisting of thin layers of cells growing between strands of connective tissue); (2) alveolar (composed of large groups of cells resembling adenoma); (3) plexiform (composed of convoluted columns showing papillary projections), and (4) diffuse (having the usual appearance of Ewing's tumor). The first three histologic types were present in the tumor in the case reported.

In discussing the theories of the origin of endothelial tumors, Ewing [6] mentioned several possible factors: (1) lymph stasis with lymphangiectasis; (2) a neoplastic growth of lymph vessels, and (3) a heteroplastic growth of lymph vessels into granulation tissue. He quoted Ribbert, who believed that lymph stasis with resultant pressure would inhibit, rather than favor, a process of growth. Certainly lymph stasis is present but whether it is a cause or a result it is impossible to say. Because of the age of the patients and other factors I prefer to subscribe to Ewing's view that the origin of lymphangioma must be attributed to a predisposition of tissue resulting from an embryogenic disturbance.

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6. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1928, pp. 252 and 334.

WHERE DOES EWING'S TUMOR ARISE?

Endothelial tumors in general are usually believed to arise from the endothelium of small blood vessels and lymph spaces. The process represents either a conversion of normal endothelium along the channels of origin into endothelial tumor cells or a diffuse overgrowth of endothelial tumor cells or both. An origin from the highly specialized endothelium lining large vessels is of course improbable on oncologic principles and has no basis of fact in the experience of pathologists. An origin from perivascular lymph spaces in the haversian canals and beneath the periosteum is thus in harmony with the origin of endothelial tumors elsewhere.

LYMPHATICS OF BONE

The information to be derived from the literature regarding the nature and distribution of lymphatic channels in bone is fragmentary and confusing. Many standard textbooks of histology and anatomy make little or no mention of this subject.

Piney,[7] Kolodny[8] and more recently Campbell[9] have undertaken to demonstrate experimentally the course of osseous lymphatics, with conclusions that are not always in harmony.

The chief point of controversy among most workers concerns the presence or absence of lymphatic channels in the bone marrow, and from the standpoint of the present paper the question is of paramount importance, because it would establish for all time the origin of Ewing's tumor.

The existence of periosteal and intracortical lymphatics is a matter of unanimity of opinion. Langer,[10] who described periosteal lymphatics in 1875, is said by Campbell[9] to have been the first to do so. Shortly thereafter Budge[11] and later Schwalbe[12] pictured a network of periosteal lymphatics communicating with intracortical lymphatics, into which Schwalbe succeeded in injecting dyes. More recently Rauber,[13] quoted by both Kolodny[8] and Campbell,[9] described the presence of

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7. Piney, A.: Carcinoma of the Bone Marrow, Brit. J. Surg. **10**:235, 1922.
8. Kolodny, A.: The Relation of the Bone Marrow to the Lymphatic System, Arch. Surg. **11**:690 (Nov.) 1925.
9. Campbell, E.: Periosteal Lymphatics, Arch. Surg. **18**:2099 (May) 1929.
10. Langer, Carl: Ueber das Gefässystem der Röhrenknochen, Vienna, K. Gerold's Sohn, 1875.
11. Budge, A.: Die Lymphwuerzeln der Knochen, Arch. f. micr. Anat. **13**:87, 1876.
12. Schwalbe, G.: Ztschr. f. Anat. **2**:131, 1877.
13. Rauber, A.: Lehrbuch der Anatomie des Menschen, ed. 9, Leipzig, Georg Thieme, 1911, pp. 5 and 17.

endothelium lining the haversian canals. Kolodny quoted Rauber, as follows:

> This endothelium forms the external wall of the perivascular lymph channels surrounding the single or multiple blood capillaries coursing in the central portion of the haversian canals. These perivascular lymphatics anastomose widely with the abundant lymphatics of the periosteum. Prussian blue injected into the periosteal lymphatics freely penetrates the substantia compacta and stops abruptly at the endosteum.

Piney [7] made injections into lymphatic channels in the periosteum. The injected materials passed into the cortical bone and thence into the endosteum, but he was unable to demonstrate any connection between the periosteo-endosteal lymphatics and the marrow. When injection was made directly into the marrow cavity, the material passed by way of definite medullary channels to the veins at the large foramina where it emerged. Piney concluded that there were no lymph channels in the marrow cavity.

Kolodny [8] agreed as to the presence of periosteal and intracortical lymphatics and himself discovered a large lymph channel in the femur of the dog which pierced the compact bone obliquely in the proximal portion of the shaft, just below the intertrochanteric line. He next conducted a series of admirable experiments designed to establish the existence of medullary lymphatics. Kolodny stated that his approach to the problem was physiologic rather than anatomic, and admitted the improbability of antomic demonstration of lymphatic channels in the bone marrow.

He injected dyes, such as india ink and carmine, into the marrow cavity in animals and recovered the material from the regional lymph nodes. The deep iliac nodes were the regional lymph nodes for the lower extremity, while the cervical nodes were said to drain the upper extremity.

A powerful clinical argument against the existence of marrow lymphatics, namely, the absence of regional lymphadenitis, was refuted by Kolodny,[8] who held that the regional lymph nodes do react, but that the proper ones are rarely examined, namely, the deep iliac and the cervical. Kolodny concluded that the bone marrow is "directly related to" the lymphatic system without offering the anatomic presence of lymph channels in the bone marrow. Piney [14] later criticized Kolodny's conclusions, saying, in brief, that the dyes could readily enter lymph nodes via the blood stream, and that this was probably the channel in Kolodny's experiments.

More recently, Campbell [9] succeeded in making injections into a plexus of periosteal lymphatics in infants and in animals. He was unable

14. Piney, A.: The Relation of the Bone Marrow to the Lymphatic System, Arch. Surg. **13**:615 (Oct.) 1926.

to demonstrate communication with intracortcial lymphatics. His method consisted in inserting the point of a fine glass cannula directly into the periosteum and injecting dilute india ink under low pressure.

Cowdrey [15] described lymphatic vessels and perivascular lymph spaces in the haversian canals.

One may conclude by saying that a great deal of histologic and experimental evidence has been accumulated; that as to the presence of periosteal and intracortical lymphatics in the haversian canals there is thorough agreement; that the existence of lymphatics in the bone marrow has never been demonstrated, and that the inconclusive evidence of Kolodny [8] has been seriously questioned.

Obviously, if there are no lymphatics in the marrow cavity, tumors of lymphatic endothelium cannot originate there. This is in keeping with the more recent anatomic studies of Geschickter and Copeland,[3] which appear to indicate that the origin of Ewing's tumors is either subperiosteal or in the cortex, *precisely the sites where lymphatic endothelium is known definitely to exist.*

Connor [5] attributed the origin of Ewing's tumor to a reticulo-endothelial cell in the bone marrow, but this conception is rather vague. Ewing has always suspected that the origin might be from perivascular lymphatic endothelium, as have more recently Geschickter and Copeland. However, in most of the material studied, the histologic picture was that of a diffuse endothelioma in which, from the nature of the structure, it was impossible to trace growth directly to lining endothelium.

I feel that the tumor in the case reported is derived from the perivascular lymphatic endothelium lying in the haversian spaces and in the subperiosteum, and that this probably represents the site of origin of Ewing's tumor in all cases. Certainly such a hypothesis would explain the early destruction of the haversian system, which is pathognomonic.

A medullary origin would seem less likely, for the reason that no one has ever demonstrated the presence of lymphatic endothelium in the bone marrow, and because the bulk of the clinical and histologic evidence is contrary to the existence of lymphatics in the bone marrow. If, as Connor suggested, the tumor arises in a primitive reticulo-endothelial cell in the bone marrow, how does one explain the absence of epiphyseal involvement in the marrow, in which reticulo-endothelial cells are surely just as numerous?

SUMMARY

1. A case is reported of a primary intracortical and subperiosteal lymphangio-endothelioma, so designated because the tumor could be traced to the perivascular lymphatics of the haversian canals and to

15. Cowdrey, E. V.: Special Cytology, New York, Paul B. Hoeber, Inc., 1928, p. 722.

those beneath the periosteum, and because the tumor cells secreted lymph.

2. The clinical course and the gross and microscopic pathologic picture of this tumor satisfied every criterion of so-called Ewing's tumor.

3. No field of pathology has been more confusing than that of endothelial tumors of the bones. This was true in the past, and is true at present, for many cases reported as instances of Ewing's tumor represent other types of growth.

4. The conception that Ewing's tumor is a primary osteolytic tumor of the medullary cavity is erroneous and should be displaced.

5. Probably in every true case, Ewing's tumor is a lymphangioendothelioma, originating in the lymphatic endothelium of the haversian canals and in that beneath the periosteum. Involvement of the medullary cavity, while prominent, is probably secondary.

6. This concept is in harmony with anatomic knowledge of the lymphatics of the bones, for lymphatics have never been demonstrated in the bone marrow, whereas perivascular lymphatics in the cortex and beneath the periosteum are well known. Even should the existence of lymphatic spaces in the bone marrow be demonstrated at a future date, the validity of the concept would not be destroyed, since medullary involvement might readily occur by transformation of normal lymph endothelium into a neoplasm.

OSTEOMYELITIS OF THE ILIUM

CARL E. BADGLEY, M.D.
Surgeon in Charge, Division of Orthopedic Surgery, Henry Ford Hospital
DETROIT

INTRODUCTION

My interest in osteomyelitis of the ilium was first aroused in 1924 when several cases with extensive chronic lesions accompanied by marked deformities of the hips came to my attention. The apparent hopelessness of these cases led me to a review of the literature on osteomyelitis of the ilium. There were surprisingly few articles on the subject in English, and these were chiefly case reports of acute osteomyelitis of the ilium and dealt with the acute phases of the disease. Two outstanding articles were found in the foreign literature, Gouillioud's and von Bergmann's, both of which advocated what seemed at the time radical measures, but which later, in the light of experience, I have accepted as sound.

My interest has been maintained in this subject for the past six years by new cases, generally of chronic osteomyelitis of the ilium, coming under observation. I am reporting 24 cases, 21 of which have been under observation for the past six years.

It is interesting to note that there is no article published, which I have been able to find after a very diligent search, dealing with *chronic* osteomyelitis of the ilium, with the possible exception of von Bergmann's, which deals in the main with acute osteomyelitis of the ilium, but also presents reports of chronic cases. There is no doubt that cases of osteomyelitis of the ilium, acute and chronic, are seen in other clinics, but with such relative infrequency that, unless some one was particularly interested in the disease, the idea of radical surgical intervention might well not be considered. From conversation with various surgeons, the impression is gained that palliative treatment, such as incision and drainage of local abscesses, possibly associated with local curettements and local resections, is the usual treatment employed.

Acute osteomyelitis of the ilium is generally regarded as a rare lesion attended with a grave prognosis. Those persons fortunate enough to survive the acute infection frequently present severe disabilities such as a chronic osteomyelitis with prolonged suppuration which may eventually lead to amyloidosis, septicemia and death. A high percentage of the survivors of the acute infection present severe lesions of the hip joint including bony ankylosis, fibrous ankylosis, or, as in three of my cases, pathologic dislocation of the hip.

The treatment advocated for acute osteomyelitis of the ilium in the recent literature seems much too conservative for cure of the lesion. In general, the trephine operation is advocated with local resections for local lesions. Resection of the ilium is generally mentioned as a possibility, but no single case was reported in which a resection was performed other than a partial resection done by Simmons.

It is of interest to note the absence of any detailed report of the further progress of the lesion in cases of acute osteomyelitis of the ilium. Several authors, Simmons and Bearse particularly, each mention a case. It would be interesting to ascertain the end-result in these acute cases in which the treatment is merely trephination of the ilium to drain an abscess in the internal iliac fossa.

Of my 24 cases, 20 were cases of chronic osteomyelitis of the ilium in which inadequate treatment by palliative and ultra-conservative measures was employed. There is a real need to present a

Incidence of Acute Osteomyelitis of the Ilium Contrasted with Acute Osteomyelitis

	Of All Bones	Of Ilium
Lannelongue	24	1
Lucke	24	1
Volkmann	29	0
Schede	24	2
Kocher	30	1
Haaga	414	4
Heidenhain	46	1
Milchner	55	3

review of the excellent work which has been done on osteomyelitis of the ilium. For there are certain known facts in regard to osteomyelitis of the ilium which place the treatment of infection of this bone on a definite basis, which, if properly followed, will give excellent results, tending to lower greatly the mortality rate, prevent invasion of the hip and sacro-iliac joints and eliminate to a considerable extent the cases of chronic osteomyelitis of the ilium. In my cases the poor results were in the failure of application of these facts, and not in the facts themselves.

INCIDENCE

Although osteomyelitis of the ilium is considered an infrequent bone infection, 20 patients were treated at the University Hospital at Ann Arbor, Mich., and another patient whose case I am reporting was treated elsewhere, between 1924 and 1929. At the Henry Ford Hospital, Detroit, 3 patients have been treated in the past two years.

Various observers have reported the incidence of osteomyelitis of the ilium in their experience (table).

Klemm reported 1,469 cases of osteomyelitis, 23, or 1.66 per cent, involving the pelvis, and 20 occurring in the ilium.

Trendel, in fifty years' experience, reported 1,058 cases of osteomyelitis with 1,279 bones involved, of which 169 were flat or short bones. Twenty-eight were in the pelvis, 25 involving the ilium. This gives approximately 2 per cent incidence of osteomyelitis of the ilium.

Frohner, in forty years' experience, reported only 4 cases involving the ilium in his series. He combined the reports of various authors, namely, Lucke, Volkmann, Schede, Kocher, Lannelongue, Haaga and Brun. From these reports he estimated that 3.3 per cent of all cases of osteomyelitis involved the flat or short bones, with 33 per cent of these involving the ilium, or about 1 per cent. Von Bergmann reported seventy-one cases of osteomyelitis of the pelvis, about sixty of which involved the ilium. His intense interest in this lesion undoubtedly was a factor in his large series of cases, the largest group ever recorded.

Monsaingeon stated that in an active service at the Clinique Chirurgicale Infantile, only 14 cases of acute osteomyelitis of the ilium were seen in thirteen years. Peeremans stated that in a hospital for children only 7 cases of osteomyelitis of the ilium, or 1.2 per cent, were seen in a total of 548 cases, but Michelson reported 137 cases in a total of 1,008, or 14 per cent, in a hospital for adults. He concluded that osteomyelitis of the ilium occurs less frequently in the prepuberty than in the postpuberty period.

AGE

The greatest incidence of osteomyelitis of the ilium is before the period of complete fusion of the epiphyses, generally before 25 years of age. Von Bergmann emphasized that osteomyelitis of the ilium also developed in older persons. In a series of 71 cases the age incidence was as follows: persons under 15 years, 12; those from adolescence to 21 years, 27; older persons, aged from 25 to 40, 21, and those older than 40, 11.

In my series 5 were over 25 years of age. However, one of the 5 had the onset of her illness at 10 years of age.

Monsaingeon stated that Cance reported the case of the youngest patient on record, that of an infant 16 days old. Broca reported a case of an infant 2 months old, and Fleury that of an infant 6 weeks old.

The usual age period is under 25, but the condition may occur at any age. My youngest patient was 20 months old and the oldest 75.

LITERATURE

The first comprehensive article on osteomyelitis of the pelvis was published in 1883 by Paul Goullioud. Entering his surgical career coincident with the development of aseptic surgery, and associated with Ollier at a period when Ollier was tremendously interested in bone infection, subperiosteal resections and bone regeneration, Goullioud was in a perfect environment for the development of his thesis. That

he took advantage of his opportunity may be attested by any one who reads his paper, for it presents the problem of osteomyelitis of the pelvis in such a complete and accurate fashion that it might well serve today as an authoritative document on this subject.

From a surprisingly accurate knowledge of the development of the bones of the pelvis, associated with Ollier's teachings of the importance of the juxta-epiphyseal zone in long bones in the development of osteomyelitis, Goullioud concluded that the bones of the pelvis may be regarded as analogous to the long bones in their skeletal development and in their susceptibility to infection. "The pelvic bones grow by cartilaginous margins as do the long bones at their ends, and the limiting parts of these cartilages correspond to the epiphyseal cartilages of the long bones." With this developmental analogy of the bones of the pelvis to the long bones, Goullioud conceived that the mechanism of infection would occur in the juxta-epiphyseal zones of the pelvic bones as it does in the long bones. With this idea as a basis, Goullioud divided osteomyelitis of the pelvis into two groups with distinct clinical syndromes corresponding to two periods of development of the bones of the pelvis. The first period extended from infancy to puberty, at the end of which period the three bones composing the acetabulum fuse. The second period commenced with the ossification of the acetabulum and the appearances of the marginal epiphyses, and extended to the time of fusion of the marginal epiphyses, at about 25 years of age.

The first period was characterized by a diffuse infection almost invariably occurring at the border of the acetabulum. This location is the site of the numerous ossification centers presenting spongy juxta-epiphyseal tissue which corresponds to Ollier's juxta-epiphyseal zone in the long bones which he felt was the most susceptible to infection. He states the infection might be periacetabular, in which case it spreads through the ilium, or it might be intra-acetabular and involve the hip joint proper. The second period was characterized by lesions occurring about the marginal epiphyses. The chief points of involvement of this late osteomyelitis of the ilium are the posterior and anterior superior spines of the ilium, the crest of the ilium and the inferior anterior spine.

Goullioud believed this classification was of great importance in the consideration of the treatment of osteomyelitis of the ilium. He felt that operative intervention for osteomyelitis of the pelvis should be more courageous. In the acute form, where the infection involved the supracotyloid area or the marginal juxta-epiphyseal area, he advocated an extensive drainage and removal of diseased bone. Where the hip joint itself was involved, he advised a resection of the ilium. In the subacute and chronic form the intervention varied with the lesion, according to its age and anatomic location.

There are many interesting historical facts presented in Goullioud's paper. He refers to Boucher, who in 1779 was the first to trephine the ilium to drain an internal iliac abscess resulting from an osteomyelitis of the pelvis. He stated that Leaute did the first recorded resection of the crest of the ilium. He reported a subperiosteal resection of the ilium performed by Larghi de Verceil in 1845, with recovery. He gives credit to Ollier for popularizing resection of bone as a proper procedure in the treatment of extensive osteomyelitis of the ilium as well as other bones, and for the important recognition that regeneration of the bone would occur if a subperiosteal resection were performed. He has collected a large number of recorded cases of osteomyelitis of the pelvis from the literature as well as reported his own cases. His bibliography is extensive.

Von Bergmann of Riga, in 1906, reported 71 cases of osteomyelitis of the pelvis in which he had treated the patients. He was greatly impressed by the scarcity in the literature of reported cases of this lesion, and by the high mortality rate. He felt that the high mortality rate occurred because the diseased area was not sufficiently excised.

He recognized that temporary cures would occur in low grade infections, either spontaneously or after palliative operations, but that after a longer or shorter period the patient would get sick again. He emphasized particularly the need of removing the diseased bone, for if not removed, it acts like a cistern for the formation of new abscesses. He therefore urged radical methods in the treatment of this lesion, with resection of all of the diseased bone.

Von Bergmann stated that Miller's hemorrhagic osteomyelitis, Brun's and Hancell's rarefying type of osteomyelitis and the diffusely infiltrating spongiosa type of osteomyelitis occur in osteomyelitis of the ilium as well as of the long bones.

He recognized the rare formation of sequestrums and the frequent perforation of the tables of the ilium. He also noted the marked thickening and sclerosis in the chronic cases of osteomyelitis of this bone.

Von Bergmann advocated the most radical measures for osteomyelitis of the ilium. He said: "The later in the disease we are called to operate, the more wide should be the resection; if earlier, we can get away with partial resection, but in youth the best treatment is resection down to the epiphyseal cartilage."

He divided the types of treatment used in his 71 cases into three main groups:

Group I: Partial resection

A. Disease of marginal epiphysis or other localized disease

Ilium	13 cases
Ischium	2 cases
Pubis	2 cases

None of these patients died.

B. Partial resection in the diffuse type
Ilium 20 cases
Pubis 1 case
Three additional cases of tuberculosis in which the patients were moribund.
In this subdivision, 17 patients died.

Group II: Total resection
There were 28 cases in this group. The hip joint was resected with the ilium in 15, and there were 7 fatalities.

Group III: Extirpation of the os innominatum and disarticulation of the lower extremity
There were 3 cases in this group, and of these 1 was fatal.

Von Bergmann felt that the mortality rate in subdivision B of group I would have been much lower had he done a total, rather than a partial, resection. He concluded that only a complete resection of the diseased pelvis could better the poor prognosis.

It is quite possible that the apparently radical nature of von Bergmann's operative treatment delayed the acceptance of the truth of his statements. A review of the cases reported in the literature since von Bergmann's report shows surprisingly few patients treated as he advised.

Monsaingeon, in 1911, reported 14 cases of acute osteomyelitis of the ilium in thirteen years' experience. He believed Goullioud's division of the disease into two age periods was what he termed very exclusive. He stated there were two main types: a subperiosteal type of lesion and a lesion involving the growing bone area, a true osteomyelitis. He subdivided the cases into three clinical groups: "(*a*) subacute type where the lesion is circumscribed in the beginning without severe symptoms either local or general; (*b*) acute type where the primary lesion is very serious, rapidly diffuse, and often accompanied by invasion of the hip; (*c*) very acute type where the general infection dominates the picture and where the local lesion is not in proportion to the severity of the infection, very probably a true septicemia type." With his theory of a subperiosteal lesion associated with an osteoperiostitis as a clinical lesion, he advocated incision and drainage in the cases of superficial subperiosteal abscesses without marked bone lesions. He advises trephining the ilium if there is an abscess of the internal iliac fossa to drain properly this abscess, or if the ilium is markedly infected. He stated that von Bergmann's results in resection were not as successful as he maintained and advocated resection only as a last resort if trephining failed to clear up the symptoms. He mentioned several rare complications of osteomyelitis of the ilium reported by various authors, citing a case of peritonitis of the pelvis following a prevesical phlegmon arising from an osteomyelitis of the ilium; a case of spontaneous rupture of an abscess from osteomyelitis of the ilium

into the rectum; a perforation of the colon in a case of sacro-iliac invasion from osteomyelitis of the ilium; several cases of severe arterial hemorrhage, and, phlebitis of the iliac vein, as well as pyarthrosis of the hip or sacro-iliac joint.

In 1915, Simmons, discussing "The Treatment of Osteomyelitis," reported 2 cases of osteomyelitis of the ilium out of 97 cases and stated that when a flat bone as the ilium is affected drainage is about all that can be done. "Many cases seen early will heal without further trouble, but if necrosis does occur, subperiosteal resection should be done in six to eight weeks." In the first case three incisions were made and abscesses drained, and later two other operations for sequestrums were reported. In the second case, a trephine operation was followed later by resection of a greater part of the ilium. Both patients had sinuses at the time his paper was written.

In 1917, Speese and Skillern reported a case of acute osteomyelitis of the ilium in which they drained an abscess in the external iliac fossa and a month later drained an abscess in the internal iliac fossa by the trephine operation, apparent recovery resulting. Geist, in 1921, remarked on the paucity of the literature on osteomyelitis of the pelvis. He reported 6 cases, 3 of which involved the ilium. He emphasized two important points: (1) that in his 3 cases the pus always collected in the internal iliac fossa, and (2) that sequestration plays little part in osteomyelitis of the ilium. Geist advocated the trephine operation. His 3 patients were reported as cured. He stated that it was necessary in all of his cases to trephine in several places through the ilium before the pus could be reached.

Peeremans, in 1923, reported 4 cases of osteomyelitis of the ilium, in which incision, drainage and removal of the outer table were done. Trephine of the iliac fossa was performed in a case. He advocated resections only in the very severe cases and felt that trephining is the operation of choice for drainage of the internal iliac fossa. It is significant that pyarthrosis of the hip joint with resultant ankylosis developed in 2 of his cases.

Bearse, in 1924, reported 2 cases of acute osteomyelitis of the ilium in which he had treated the patients. He concluded: "If the ilium is perforated, incision and drainage is sufficient; with no perforation or unsatisfactory bone drainage, trephine operation of the ilium should be done. If, however, the process is an extensive one, partial or total resection should be done." In one case he used incision and drainage, and the wound was still draining at the time of his report; in the second case there was a perforation which he enlarged.

Koulouch, in 1924, reported a case in which the abscess was located in the internal iliac fossa and was drained directly on the inner side of the anterior superior spine. One and one-half years later he exposed

the ilium on both sides subperiosteally, finding a sequestrum posterior to the anterior superior spine and another in front of the sacro-iliac joint. A third sequestrum was found on the external surface just posterior to the acetabulum. There were several fistulas through the bone. All diseased bone was removed, but resection was not done as it was considered too radical a procedure.

Buonsanti, in 1924, reported in his experience 4 cases of acute osteomyelitis of the ilium with a mortality of 3, or 75 per cent. He emphasized the high frequency of an abscess in the internal iliac fossa, suggesting as possible factors that the pelvic periosteum perforates more easily and the iliac muscles strip more easily and the inclined plane of the pelvis tends to drain toward this fossa. He stressed the lack of spread of the infection to the viscera by continuity and gave credit to the pelvic diaphragm for preventing drainage into the true pelvis. He advocated incision and drainage in the very severe cases as a preliminary measure, quoting Professor Gatti: "Opening the wound helps not only the local but the general condition of the patient, attenuating the germs in the focus and removing just that much of the general symptoms due to the enclosed focus." In the diffuse cases he recommended trephining as practiced by Condamin. He believed resection should be done in the extreme case in which the squamous portion is bathed in pus.

Flickinger, in 1927, reported a case of osteomyelitis of the ilium for two reasons: first, because of the infrequency of a report of this type of case, and secondly, because no results after hospitalization have been reported.

In 1928, one of Cabot's case records contained a discussion on the differential diagnosis in a case in which the diagnosis of osteomyelitis of the ilium was not made until a biopsy done for the possibility of tumor demonstrated the inflammatory nature of the lesion.

This concludes a complete survey of the literature on this subject. As most of the articles are in a foreign tongue, and the work of several authors is so outstanding, a more comprehensive review than usual is given.

DEVELOPMENT

There is a single center of chondrification for each of the three bones composing the hip bone. These centers soon fuse to produce a continuous cartilaginous hip bone which gradually assumes a definite form. An excellent conception of the cartilaginous anlage of the hip bone may be obtained from figures 1 and 2. A center of ossification appears in the main body of each of the cartilages, appearing first in the ilium (fig. 1), secondly in the ischium and lastly in the pubis. All three ossifying centers are shown in figure 2. The rami of the

ischium and pubis are united by bone in the seventh to eighth year. In the acetabulum the three bones composing the hip bone are separated by a Y-shaped cartilage until after puberty. The os acetabuli appears in this cartilage between the ilium and the pubis between the ninth and twelfth years. Union of the os acetabuli to the pubis occurs about puberty and soon afterward the acetabular portions of the ilium, ischium and pubis fuse.

Fig. 1.—Five months old fetus showing ossification in the ilium but no ossification in the remainder of the pelvis. The cartilaginous continuity of the pelvis is well shown. (Published, by permission, from the article by Rudolph Skarda: J. Tech. Methods, to be published.)

Two secondary ossification centers for the ilium appear at about puberty, one for the crest of the ilium, and the other for the inferior spine of the ilium. The marginal epiphysis for the crest runs from the anterior superior spine of the ilium to the posterior superior spine. The appearance of the hip bone at puberty is well demonstrated in figure 3.

These secondary epiphyses fuse somewhere between the twentieth and the twenty-fifth year.

ANATOMY

It is impracticable to give a detailed anatomic description of the ilium, but there are several anatomic points which properly should be stressed. First, the structure of the ilium is irregular. The thicker parts of the bone consist of cancellous tissue enclosed within two layers of compact tissue which are lined by periosteum. The thinner parts, as at the bottom of the acetabulum and the center of the iliac fossa, are so thin that they are usually semitransparent and composed entirely of compact tissue.

Second, the internal and anterior sloping of the internal iliac fossa with its termination at the ileopectineal line is of great importance in explaining the great prevalence of abscess formation in the internal iliac fossa and the tendency to point anteriorly in Scarpa's triangle; blocked from passing further into the true pelvis by the structures attached to the ileopectineal line, gravity forces the purulent collection forward rather than backward.

ETIOLOGY

The organism which is chiefly responsible for osteomyelitis of the ilium is Staphylococcus pyogenes-aureus. The causative agent is rarely Stapyhlococcus albus, occasionally the pneumococcus, and infrequently the streptococcus. In the vast majority of reported cases and in practically all of my cases Staphylococcus aureus was the organism isolated. In one case tuberculosis was also recorded.

TRAUMA

Trauma undoubtedly plays some part in the development of osteomyelitis of the ilium. Bounsanti believes that the ilium is most frequently involved in an osteomyelitis of the pelvis because it is the most exposed to trauma. Definite trauma is frequently cited in the history, and was quite frequently reported in my cases.

PATHOLOGY

Goullioud was the first to recognize that the ilium did not differ essentially from the long bones in the anatomic structure. If one considers the epiphyseal structures of the ilium, the bone is quite analogous to a long bone with its shaft and epiphysis. Juxta-epiphyseal zones with areas of rapid ossification centers exist in the ilium as in the long bones. Infections localize in these areas exactly as Ollier has demonstrated their presence in the juxta-epiphyseal regions in the long bones. Later, Lexer's work with the injection of the nutrient vessels demonstrated the rich vascular plexus about the juxta-epiphyseal regions in the ilium, corresponding to the similar areas in the long bone (fig. 4). According to Lexer, the chief nutrient vessel enters the ilium on its

visceral side at the posterior portion of the arcuate line, passes forward and upward, and then bends sharply from above toward the acetabulum. It soon divides into numerous larger branches which quickly spread in all directions as fine branches. These branches reach upward toward the edge of the iliac fossa and downward toward the acetabulum. The acetabular part of the ilium receives the lowest tuftlike disseminated branches.

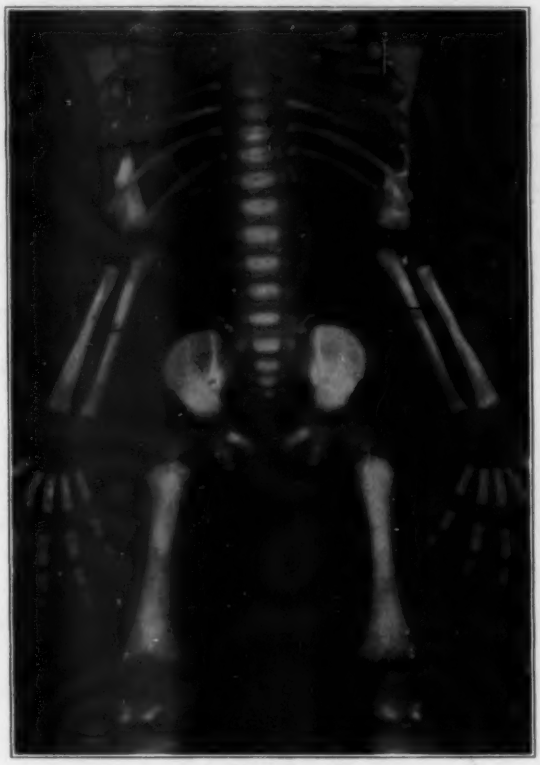

Fig. 2.—Five and one-half months old fetus showing calcification quite advanced in the ilium. Calcification is now present in the ischium and the pubis. (Published, by permission, from the article by Rudolph Skarda: J. Techn. Methods, to be published.)

It has been fairly well accepted that acute hematogenous osteomyelitis develops primarily in the dilated tufts of the metaphyseal vessels if the infected emboli are small, producing local areas of osteomyelitis. If larger, the nutrient vessel itself may become plugged, producing extensive necrosis of the bone dependent on it for nourishment. This extensive necrosis of bone rarely occurs in the ilium because of the rich blood supply introduced by the periosteal vessels. The architecture of

the ilium with its thin external and internal plates of cortical bone lined with periosteum and the small amount of spongy bone between aids greatly in prevention of massive sequestration.

Wilensky, in discussing the mechanism of acute osteomyelitis, spoke of the flat bones as structures derived exclusively from periosteal formation and from two opposing periosteal surfaces. He stated:

> Practically speaking, the blood supply of the bone is a double periosteal vascular network. The nutrient artery circulation is negligible. The form of osteomyelitis which develops is determined by the physical characteristics of the vascular network; periosteal and subperiosteal forms of inflammation are the *rule*. A dominant characteristic of osteomyelitis of a flat bone is that its development immediately destroys the osteoblasts that are present. This explains the absence of any new bone formation. The extreme of this occurs when a defect occurs in the entire thickness of the skull bone; the defect remains permanently.
>
> Under ordinary circumstances the integrity of the bone is preserved by the physical part of the double periosteal origin of the bone; circulation and repair is maintained from the opposing surface to that in which the inflammation is seated; and, as in other bones, the amount of destruction is limited to a superficial sequestration.

I cannot agree with Wilensky's statements in regard to osteomyelitis of the ilium. The ilium is not formed from periosteum but develops in cartilage from an ossifying center. The periosteum undoubtedly plays a part in its development, but it is essentially a bone formed from cartilage. The nutrient artery is not negligible as Lexer's injections demonstrate. Entrance of infection through the nutrient artery, at least until puberty, is probably the rule, as the vast majority of cases occurring before puberty show a diffuse osteomyelitis developing about the acetabulum in the zone of greatest vascularity of the nutrient vessel in the analogous juxta-epiphyseal region of the long bones. Monsaingeon has noted clinically a type of osteomyelitis which he classified as a periostitis with subperiosteal abscess formation. Monsaingeon also quoted Kirmisson and de Rocher, who believe that the periosteum itself may be the primary focus. This agrees with Wilensky's views. The frequency with which extensive bone changes developed in Monsaingeon's cases of supposed primary periosteal lesion weakens his theory of origin. The frequent evidence in reported cases of osteomyelitis of the ilium of perforation of one or the other table of the ilium or of both tables indicates that these abscesses are often formed within the cortices of the ilium and become subperiosteal from perforation rather than from a primary periosteal lesion. It is well known that a primary periosteal infection of the long bones occurs infrequently in contrast to the well recognized metaphyseal origin of the osteomyelitis with a subperiosteal abscess formation developed by the draining outward of the pus. Why should the ilium differ so radically from the long bones? Von Bergmann in

this connection stated that should one make simply a diagnosis of infected periostitis in these cases and not make any further observations on the bone, the patient would not be helped by a simple incision. The softened bone which is left behind is always the cistern for formation of new abscesses. The softening spreads farther to involve the other two components of the os innominatum, and either the hip joint or the sacro-iliac joint becomes infected.

In my cases of chronic osteomyelitis of the ilium, I did not note the absence of new bone formation that Wilensky described. In many cases involucrum formation was most extensive with numerous large and

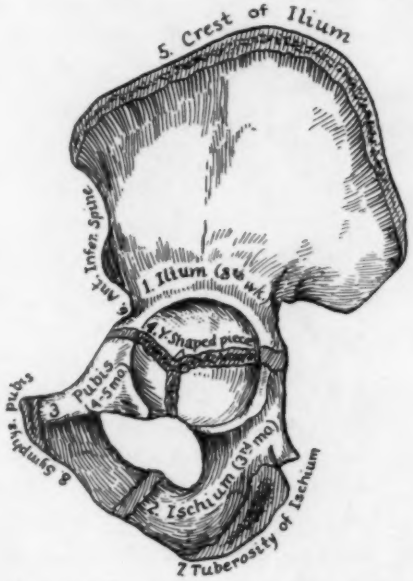

Fig. 3.—Ossification of the hip bone at about 13 years of age. (From Gray: Anatomy, Descriptive and Applied, Philadelphia, Lea & Febiger, 1924.)

small abscesses lined with dense eburnated bone. Sequestration of any great size was very rare, although in several cases numerous sequestrums were recovered. The lack of large sequestration can be easily explained by the thin cortical structure of the ilium, which by its structure could not make a sequestrum of any great thickness. The cortex is so thin that sequestrums formed could easily be digested by autolytic ferment, caries and phagocytosis.

I feel that the absence of extensive sequestration in the ilium is due not to the fact that the nutrient artery is never completely plugged, but to the generous blood supply of the double periosteum and its ability to nourish and develop bone. It is chiefly in this characteristic that osteomyelitis of the ilium differs from osteomyelitis of the long bones.

There are essentially two types of acute osteomyelitis of the ilium, one, a localized type, and the other, a diffuse type. Goullioud's observation that osteomyelitis of the ilium may be classified as the prepuberty and postpuberty types is in general sound. The diffuse type, arising in the periacetabular region and diffusing through the ilium and frequently into the hip joint or less frequently invading the sacro-iliac joint, occurs in the prepuberty type. The localized type occurs after puberty in the region of the marginal epiphyses, generally in the anterior portion of the ilium and less often in the posterior portion where sacro-iliac invasion sometimes occurs. Rarely is the crest itself involved, and primary periostitis is a rare occurrence.

With the exception of sequestration, the same pathologic process is present in osteomyelitis of the ilium that is noted in other bones. Two outstanding features should be observed: first, the frequent tendency to perforation, and second, the great tendency of an abscess to develop which points in the internal iliac fossa, stripping the visceral periosteum and the iliacus muscle from the internal table, and then tends to gravitate into Scarpa's triangle, posteriorly to the sacro-iliac joint or posteriorly at the triangle of Petit or at the greater sciatic notch. The absence of massive sequestration is also characteristic.

DIAGNOSIS

The diagnosis of acute osteomyelitis of the ilium is made difficult by several factors. First, the patients are acutely ill, and in many cases profoundly so; the general symptomatology frequently overshadows the local lesion, and the patient, dull and apathetic, does not offer much aid. Second, in the diffuse type of osteomyelitis of the ilium the lesion is situated so deeply from the surface that local palpation is not often of value. The local marginal involvement about the crest will frequently demonstrate tenderness on palpation, and the diagnosis of this type is much simpler. Third, the close proximity of the hip joint to the site of the infection associated so frequently with symptoms of involvement of the hip joint makes it difficult to differentiate between an acute osteomyelitis of the ilium and a pyarthrosis of the hip. Under guarded movements in osteomyelitis of the ilium, not involving the hip, a range of motion will be obtained which would be inconsistent with a pyarthrosis. Also, the deformity of a pyarthrosis of the hip is a flexion, abduction and external rotation, whereas in osteomyelitis of the ilium without pyarthrosis, the deformity tends chiefly toward flexion. Fourth, a frequent factor in the failure to recognize osteomyelitis of the ilium is undoubtedly its relative infrequency which makes one forgetful of its possibilities. This diagnosis should always be considered as a possibility

in a patient with high fever, leukocytosis, pain in the region of the hip, guarded motion of the hip and possibly local tenderness over the ilium.

Errors in diagnosis of this lesion are common. In my series a large number of the patients were thought to have typhoid fever. Tuberculosis is frequently blamed, and rheumatism is often a diagnostic error. It is not unusual that patients with acute osteomyelitis of the right ilium are operated on for acute appendicitis. The most important differential diagnosis, however, lies in the distinction between osteomyelitis of the ilium, pyarthrosis of the hip and osteomyelitis of the upper third of the femur. Absence of tenderness along the shaft of the femur and

Fig. 4.—Nutrient vessel of the ilium. From Lexer's "Untersuchungen über Knochenarterien."

ability to move the hip, if motions are gently performed, point to osteomyelitis of the ilium.

In its clinical appearance acute osteomyelitis of the ilium may be divided into three types as described by Monsaingeon.

Type 1.—This type is localized osteomyelitis of the ilium, involving the areas about the crest or the spines of the ilium. The onset is of moderate gravity accompanied by a much less intense general reaction. The localization of the symptoms is quite definite, and because of the superficial location of the lesion, early abscess formation is noted. Diagnosis is much easier in this type of case, and treatment can be instituted much earlier. As the parts are easily accessible, the treatment

generally is adequate. These cases are most frequently seen in the postpuberty stage.

Type 2.—The diffuse type of osteomyelitis of the ilium, seen generally in the prepuberty period of life, is characterized by a much more severe local and general reaction with quite profound toxemia. Local symptoms are marked, but the general reaction is generally severe.

Type 3.—This type shows a most profound general reaction with the local symptoms insignificant in comparison. A septicemia with visceral metastases is generally present, and the osteomyelitis of the ilium is merely one of the local manifestations of severe and generalized infection.

SIGNS AND SYMPTOMS

The local symptomatology of osteomyelitis illustrates certain factors of importance in recognizing this lesion. Pain is the outstanding symptom and is generally felt in the hip, frequently in the region of Scarpa's triangle. Occasionally the pain is felt posteriorly, about the sacro-iliac joint and may be referred along the sciatic nerve (Kolouch's case). Geist emphasized the fact that in his three cases the pain was referred to Scarpa's triangle, and there was no pain in the internal iliac fossa with abscesses in this fossa. The deformity is an important sign in the differential diagnosis. With pyarthrosis of the hip joint there is generally a marked flexion, abduction and external rotation deformity. Any attempt at change of this position is resisted by the patient. In osteomyelitis of the ilium, with an abscess of the internal iliac fossa, there is a tendency to assume this same deformity. However, this deformity is much less marked and is chiefly flexion. Motion of the hip can be performed gently with the chief restriction in extension.

Tenderness to palpation is of definite value in the localized marginal lesions. Occasionally palpation reveals marked bony tenderness in the supracotyloid area. A diagnosis on such a finding was substantiated by roentgenograms and operation by Dr. V. L. Hart (verbal report) at Ann Arbor recently. Palpation should be made on either side of the ilium. In the chronic cases, one often feels a thick indurated swelling in the internal iliac fossa which is tender to palpation and which has not previously been noted by the patient. Rectal examination will frequently disclose swelling on the affected side of the pelvis which could not have been palpated in front.

The frequency of swelling in Scarpa's triangle should be noted in the subacute cases. Induration about the ilium associated with edema, prominence of the superficial veins and local heat can be made out occasionally.

The general findings of osteomyelitis elsewhere are seen here in that the temperature is high, chills are frequently recorded, there is a rapid pulse rate, and a high polymorphonuclear leukocytosis is generally present.

ROENTGEN EXAMINATION

In the acute case roentgen examination is of little value. With the improved soft tissue technic of today, one can occasionally visualize soft tissue swelling lateral to the outer cortex of the ilium, which aids somewhat. The roentgenograms taken later in the disease first show a mottled appearance with loss of sharp detail generally noted in the ilium. Later, the marked osteosclerosis, the so-called "marble appearance," is demonstrated. In my experience this generally means abscess formation lined by eburnated bone. Sequestration is rarely seen in roentgenograms. The changes noted in the roentgenograms in the chronic cases are frequently bizarre and make the diagnosis difficult from the roentgenologist's standpoint. A recent case record of Cabot in which a chronic osteomyelitis of the ilium was diagnosed as a sarcoma illustrates this difficulty. However, a good conception of the chronic case can often be obtained by roentgen examination, especially in the localized cases. Perforation is frequently noted on roentgen examination.

The localized abscesses just above the acetabulum in two of my cases are excellently demonstrated by roentgenogram (figs. 7 and 9).

In the chronic case the diffuse type of osteomyelitis of the ilium shows a dense thickened bone with areas of rarefaction here and there, and frequently bony overgrowth can be demonstrated on the external surface of the ilium (fig. 11).

TREATMENT

The treatment of osteomyelitis of the ilium may be divided into three phases of the disease: the acute, the subacute and the chronic stages.

The treatment of the acute phase is subdivided as to whether it is a diffuse or localized osteomyelitis. As Goullioud has shown, the age of the patient is of considerable aid in determining this point. The cases of the prepuberty type are generally diffuse, and the osteomyelitis begins in the pericotyloid region. The cases of the postpuberty type are generally localized, and the disease begins about the marginal epiphyses. Monsaingeon's subdivision of the acute group into the three types is as follows: (*a*) subacute or localized lesion, (*b*) acute or diffuse osteomyelitis and (*c*) very acute diffuse osteomyelitis with probably generalized septicemia.

These divisions have already been described. In type *a* localized to the marginal epiphyses it is wise to incise, drain and eradicate the

involved bone to establish free drainage outward for the bone itself. Simply draining the abscess might be sufficient in a low grade infection, but a virulent infection might spread rapidly in a very few hours throughout the squamous portion of the ilium. I do not advocate extensive resection in the early stages, but feel it is necessary to expose thoroughly the involved bone area so that infection in the bone will not develop pus under pressure and so that free exit of pus is secured. Later in the progress of the disease a localized resection of the involved area may be necessary. This type of localized involvement is the most favorable for treatment.

Type *b* is the diffuse type in which the patient is seriously ill. Here one must consider the general condition of the patient as well as the local condition. Starr stated that the early acute stage of inflammation with pressure from exudates is always accompanied by the clinical symptoms of pain and intense toxemia. This is also the stage of greatest danger from septicemia. "Early drainage with relief of pressure alleviates the clinical symptoms." I believe it also lessens the chance of a septicemia. In the early acute stage there will be no abscesses outside of the bone, so one must be prepared to enter the bone on the strength of one's diagnosis. The external table should be exposed by the Larghi method. It is in this type of a case that the trephining of the ilium above the acetabulum is of greatest value. It opens directly into the very seat of the infection and tends to drain both the interior of the bone and the internal iliac fossa. It can produce little harm in case the diagnosis of early osteomyelitis is wrong. This is essentially the function of the trephine operation and not, as has been advised by most authors, its employment for drainage of a recognized internal iliac abscess.

When acute osteomyelitis of the diffuse type has progressed a few days there will be in many cases a spontaneous perforation of one or the other table of the ilium with an abscess formation subperiosteal in either the internal or the external iliac fossa. This occurs by far most frequently in the internal iliac fossa. If this abscess is recognized clinically, one need not consider the trephine as a diagnostic measure. Osteomyelitis at this stage is much more extensive than in the early case, and the prognosis is more grave.

In this case it is wise not to attempt a questionably satisfactory drainage by trephining through the wing of the ilium as is commonly advised.

If the patient is extremely toxic, it might be well first merely to drain the abscess, drainage done by subperiosteal reflection of the internal table directly to the abscess in the internal iliac fossa being the method of choice. Then in a few days, when the patient is in better

physical condition, proceed with the more radical bone operation. However, if the patient's condition will tolerate it, it is better to do the radical operation at once without the preliminary drainage. The ilium should be exposed subperiosteally on both tables to the arcuate line. Resection of the wing of the ilium to the supracotyloid portion is easily and quickly done by rongeur or osteotome. The diseased bone should be removed and resection as extensive as necessary should be carried out. The disease rarely extends into the hip joint, but in such cases complete extirpation of the ilium should be done. As von Bergmann demonstrated, this can be done in patients under 13 years of age by avulsion as the cartilage of the ilium has not yet fused to the ischium and the pubis. Generally, however, in these early cases, it will be necessary only to remove the ilium to the periacetabular region. Adequate drainage is then established, regeneration of the ilium follows, and hope of a complete recovery without recurrence is good (case 1). This operation is no more shocking and no more difficult than the trephining operation. In case 1, the total time for the operation was twenty minutes.

This procedure of adequate drainage of both the abscess and the bone infection offers the patient not only the best chance for life, but a good chance for a permanent cure of the infection.

Type *c* is the diffuse type with an extensive overwhelming general infection. Whatever treatment one employs will be open to criticism. I feel certain in this group, however, that the only chance is in raising the patient's resistance by eradication of all possible local involved areas. In spite of the extremely high mortality rate in this group, the resection of the ilium is indicated in these cases.

SUBACUTE OSTEOMYELITIS OF THE ILIUM

The treatment of the subacute form of osteomyelitis of the ilium should be differentiated into the localized and the diffuse type. As the roentgenograms are of great value here, it is possible at this stage to have quite a definite idea as to the extent of damage and the location of the lesion. In the local type, local resection of the involved area is easily carried out and should be the operation of choice. In the diffuse type, one may do either a resection of both tables or a removal of the outer table and diseased bone to the inner table. The best procedure is complete eradication of both tables, and there is more certainty of a complete cure. One point which should be emphasized here is that one cannot wait for sequestration to occur as is frequently advised in subacute osteomyelitis in long bones. The problem is quite different. In osteomyelitis of long bones the continuity of the shaft must be maintained for weight-bearing. Therefore, one is very reluctant to

remove viable bone. The wing of the ilium is not essential for function and can be sacrificed if necessary. Sequestration does not occur here as in the long bones, but multiple diffuse abscesses with occasional small sequestrums are present. With complete resection all diseased bone is removed, and during regeneration in all probability a new healthy ilium will form.

CHRONIC OSTEOMYELITIS OF THE ILIUM

Chronic osteomyelitis of the ilium is a problem in itself. I have attempted removal of the outer table only, with complete saucerization of the abscesses, but a diseased area is apt to be left behind. The tremendous thickening that occurs in the ilium in chronic osteomyelitis makes it difficult to tell when one is near the inner table, and frequently there are abscess cavities under the inner table perforating into the iliac fossa. The operation of resection is not much more difficult or shocking than saucerization, and I would advocate resection of both tables. It is rarely necessary to do a complete resection in the chronic case. When the wing of the ilium to the supracotyloid region is removed, diseased bone in the body of the ilium can be eradicated by curettement and saucerization to healthy bone. The situation is ideal for saucerization, as the visceral muscle group and the gluteal group completely obliterate the cavity.

POSTOPERATIVE TREATMENT

In the greatest number of my cases I have kept the wound wide open with packs, using the Carrel-Dakin method. Thus, the wound has granulated in from the bottom. Lately I have used treatment with gauze smeared with petrolatum and have been greatly pleased with the results. Secondary closure of the wound has been done in a few of the cases with a much better resultant scar.

TECHNIC OF RESECTION OF THE ILIUM

An incision is made just below the crest of the ilium, extending from the posterior superior spine of the ilium to the anterior spine and is then extended onto the thigh lateral to the sartorius. The fascia is cut through about one-half inch below the crest, the muscles are stripped close to their attachment to the crest, and the periosteum is incised along the line of the skin incision close to the crest. By subperiosteal reflection with a sharp periosteal elevator, the gluteal muscles are stripped down to the acetabular rim. The interval between the tensor fascia femoris and the sartorius is exposed to allow retraction of the gluteal muscle mass. The anterior portion of the ilium is exposed by this subperiosteal dissection. In children the cartilaginous crest of the ilium may be detached easily with the abdominal muscle insertions still

attached to it. In older persons von Bergmann advocated chiseling off the crest of the ilium to maintain these attachments. I have found it simpler and as effective to continue the subperiosteal dissection over the crest of the ilium, separating the abdominal muscles, the latissimus dorsi, the quadratus lumborum and the spinae erectae from their insertions. When this has been completed, the abdominal contents fall away, exposing the wing of the ilium beautifully. The inner table is then stripped subperiosteally to the arcuate line of the ilium. The falling away of the abdomen makes retraction very simple (fig. 15).

In the chronic case this subperiosteal dissection will be somewhat difficult because of scarring due to perforation and involucrum, but the stripping can be done if one is patient and persistent. Hemorrhage is a negligible factor as long as one keeps the dissection beneath the periosteum.

To obtain a better exposure, the sartorius and Poupart's ligament may be stripped from the anterior superior spine.

One may then remove the ilium to the supracotyloid region *en masse* by motor saw or osteotome, if necessary back to the sacro-iliac joint. In the chronic cases, I define the extent of the lesion and remove the involved area *en masse* if possible. In the acute cases I rongeur through the ilium to note the extent of the infection, progressing through diseased bone to what is considered normal bone.

If it is felt that a patient with an internal iliac fossa abscess is too ill for such an operation, drainage of the abscess by an incision through the anterior third of the ilium with subperiosteal dissection of the internal table into the internal iliac fossa direct is advocated. Later, if the patient responds to this drainage, more radical exposure of the ilium can be performed.

If the posterior portion of the ilium or the sacro-iliac joint is chiefly involved, I have used the approach to the ilium which Smith-Petersen employs for arthrodosis of the sacro-iliac joint, but I have also resected the posterior third of the ilium. In several cases I have combined the anterior and posterior approaches for a complete exposure of the ilium. By removing the ilium posteriorly, a perfect exposure of the sacro-iliac joint is made which gives the best drainage possible for this joint.

RÉSUMÉ OF THE TWENTY-FOUR REPORTED CASES

The age incidence in my reported cases varies from 20 months to 70 years of age. Four of the patients were over 25 at the onset of their infection. Only 4 of the cases could be classified as in the acute stage and would fit better in the subacute stage, as four weeks had elapsed before I saw them. The longest period from onset of the infection until I saw the patient was twenty-five years, another was

nine years and another eight years. Eleven patients gave a definite history of trauma which bore a close relationship to the onset of the infection.

There were 18 males and 6 females in this series, ratio of 3:1.

Serious involvement of the hip joint occurred in a large proportion of the cases, bony ankylosis occurring in 9, fibrous ankylosis in 2 and pathologic dislocations in 3. The presence of the pathologic dislocations in 2 cases was apparently the result of the patient's splinting the abducted hip with the well leg, throwing the well hip into adduction, flexion and internal rotation with a resultant dislocation of the well hip. These cases led to further study with my former associate, Hart, of the mechanics of pathologic dislocation of the hip, and our study was recently published by him.

There were marked symptoms of hip irritation noted in cases 3 and 7, an abscess cavity being present in both just above the acetabulum. The patient in the first case recovered with no involvement of the joint, but in the second a stiff hip developed following an operation performed elsewhere.

In 3 cases (cases 1, 22 and 11) of acute diffuse osteomyelitis of the ilium, the hip was not involved, although marked irritation of the hip was present clinically. Radical resection or removal of the outer cortex of the ilium for drainage was employed.

In 5 other cases the hip was not involved because the lesion was local and involved the anterior third of the ilium. Two cases involved the posterior third of the ilium and invaded the sacro-iliac joint, not affecting the hip.

In my series there were 14 cases of diffuse osteomyelitis of the ilium. Ten of these patients were 14 years old or younger. One of the remaining four was 17, and in this case the infection of the ilium was a secondary lesion to a multiple osteomyelitis. Another patient was 16 years of age, and two were 15 years.

There were 10 patients with the localized type of osteomyelitis of the ilium, 9 of whom were 15 years of age or over.

These facts certainly strongly substantiate Goullioud's prepuberty and postpuberty divisions as a means of deciding whether the lesion is diffuse or local.

In my series of 24 cases the final results were seen. Two deaths occurred, one from chronic suppuration followed by amyloidosis with brain abscess as the terminal picture.

In 1 case (case 15) a recurrence of infection in the posterior third of the ilium was reported three years after operation. The patient in case 24 is in excellent health, but has a small sinus with little discharge. A total resection would have been a better procedure in her case. The patient in case 12 still has a discharging sinus and some activity, but

he is greatly improved generally. In case 18 the patient is greatly improved but still has a small sinus. In case 20 there was great improvement, but the resection was not sufficiently extensive.

Resection of the wing of the ilium was done twelve times, partial resection of the anterior or posterior third in 5 cases, removal of the outer table of the ilium accompanied by saucerization of the ilium in 4 cases, sequestrectomy and drainage in 1 and saucerization of an abscess just above the acetabulum in 2.

Seventeen of the 24 patients have been completely cured. By cured, I mean the sinuses have become obliterated, the patient's general health has returned to normal, and he is apparently well. Some of these patients have remained well for years, others for shorter periods. It is possible that they may have some recurrence, but the picture now is entirely different from that when they first consulted me.

REPORT OF CASES

CASE 1.—J. L., a boy, aged 20 months, entered the Henry Ford Hospital on Aug. 5, 1929, and was discharged September 19. Four weeks before admission a "boil" was noticed over the right thigh and was opened by the mother a few days later. Fever developed, and the child was severely ill, his temperature being 104 F. A small abscess developed over the crest of the ilium, which was lanced by the local doctor, and dark blood was obtained. The fever persisted. Roentgenograms showed a destructive process in the ilium a week before admission.

On examination the child was profoundly toxic and apprehensive. The right leg was held in abduction, flexion and external rotation, and there was marked muscle spasm. Gentle motion allowed a fair range of movement. There was marked tenderness above the trochanter and about the ilium with thickening and tenderness on palpation on the mesial side. Leukocytes were 14,500, and the temperature was 101 F.

A roentgenogram showed a mottled appearance of the ilium with a traveling acetabulum and one area which looked as though it might perforate into the hip joint. The roof of the acetabulum was displaced upward, and the head appeared partially subluxated.

The child was given fluids intravenously, and operation was performed on August 7. Incision from the anterior superior spine of the ilium to the posterior spine carried through to the bone. Subperiosteal reflection of the external table was done. There was no evidence of pus externally, but on breaking through the cortex a few drops of pus were found in the posterior angle of the ilium. The cartilaginous rim was removed from the crest after von Bergmann's method with the abdominal muscles intact. The inner cortex of the ilium was exposed, opening into a large abscess cavity filling the internal iliac fossa which drained profusely. Numerous cloacae opened from the internal table to this abscess. The ilium was removed by rongeurs, leaving only a little of the anterior and the posterior portions down to the arcuate line of the ilium.

The spongy bone left behind seemed normal. The wound was left wide open, and Carrel-Dakin's treatment instituted. Traction was applied to the hip. The child did remarkably well and was discharged on September 19, with the wound almost healed. The hip was entirely free from symptoms. On Feb. 21, 1930, the

patient reported back with a draining sinus in the posterior angle of the wound. The hip was normal clinically, and the child walked without a limp. A roentgenogram showed a suspicious area just above the acetabulum. Operation was advised, but the sinus healed shortly after this.

A letter from the patient's home doctor in January, 1931, stated that the sinus healed in a few weeks, and that the boy has been well since.

CASE 2.—F. C., a man, aged 24, entered the Henry Ford Hospital in August, 1929. Nine years before admission he fell, striking the right hip and side. They were quite painful at the time, but he was able to walk home, a distance of 2 miles. The tenderness and soreness left in a few days. Six months later, while playing hockey, he was struck over the brim of the pelvis by the puck. Immediately the area of the pelvis became blue and swollen. The physician was of the opinion that the lesion must have been present prior to the injury in order to produce such a sudden reaction. The patient was operated on; pus was found in the soft tissues,

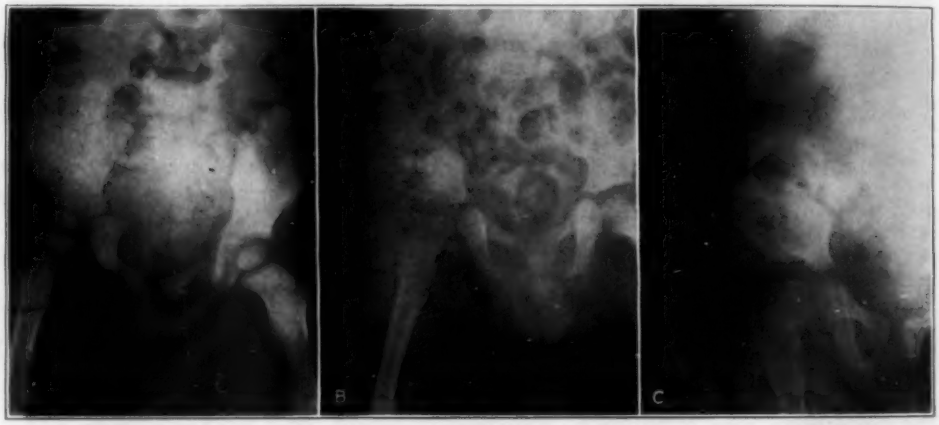

Fig. 5 (case 1).—Roentgenogram showing *A*, the typical mottled appearance seen in osteomyelitis of the ilium in the early stage. This was taken from three to four weeks after onset. Note the traveling of the acetabulum and the destruction chiefly in the periacetabular region. This is the usual site of origin of infection in the diffuse type of osteomyelitis. *B*, roentgenogram taken after operation. Extensive resection of the ilium to the body had been performed. The body portion was then given perfect drainage. Note the improved appearance of the hip joint. *C*, roentgenogram showing extensive regeneration of the ilium six months after operation. The hip joint looks quite normal. Note the improvement in the periacetabular portion of the ilium.

and the bone was found to be infected. Curettement and drainage were done. The wound healed, but would break down and discharge at intervals. The wound had been healed for as long a period as two or three months. The patient is a semiprofessional boxer, and blows in the ring precipitated drainage. The lesion interfered with his boxing and although he felt well, he wanted this corrected.

Physical examination showed an old scar over the crest of the right ilium with a small draining sinus in the inguinal region. Under the medial to the anterior superior spine of the ilium there was also an old healed sinus. Examina-

tion at that time showed marked thickening of the wing of the ilium and local tenderness. The patient was a very well built, well appearing man.

He was operated on in October, 1929. The anterior two thirds of the ilium was exposed with difficulty because of massive involucrum formation and was removed by means of an osteotome. Numerous abscesses were found throughout the ilium, one in the anterior superior spine pointing toward the sinus. Five abscesses were found in the wing of the ilium. The wound was packed wide open with gauze treated with petrolatum. No sequestrums were found, but the ilium was almost five times the normal thickness, hard and eburnated with numerous walled off abscesses.

On December 29, a secondary closure was performed which healed by primary intention.

In January, 1931, at the time of the last observation, the patient had been entirely free from difficulty since operation. He is a professional boxer and had engaged in a bout every six weeks for the past six months. Roentgenograms taken at this time showed almost complete regeneration of the ilium.

Fig. 6 (case 2).—*A*, roentgenogram showing extensive involvement of the anterior two thirds of the ilium, chronic osteomyelitis with abscess formation and perforations. Note the absence of involvement about the periacetabular region. This is the local bone lesion seen in the postpuberty stage. *B*, roentgenogram taken following resection of the diseased bone. Gas in the bowel causes the apparent rarefaction in the remaining portion of the ilium. Note how sharply one may resect out the involved area in chronic localized osteomyelitis of the ilium. *C*, roentgenogram showing regeneration following resection one year after operation.

Case 3.—R. M., aged 21, a college student, entered the University Hospital in September, 1926, with pain in the right hip of two weeks' duration. There was a recurrence of symptoms in February, 1927, of one month's duration, but severe enough to take the patient out of school for a semester. He had another attack of two days' duration last summer. The last attack began on March 22, 1928, with a painful hip. The leg was held in a position of abduction, flexion and external rotation with muscle spasm and limitation of motion in all directions. The temperature on admission ranged from 99.6 to 102.2 F. The leukocyte count was 16,000, and there were 4,800,000 red blood cells. The hemoglobin was 87 per cent and polymorphonuclears 78 per cent.

Stereoscopic studies of the right side of the pelvis demonstrated several well defined areas of rarefaction with a sclerosed border in the lower part of the ilium just above the acetabulum. No involvement of the hip was noted.

Operation was performed on April 2, and the anterolateral approach was used. The ilium was exposed and pus was found between the gluteus medius and tensor fascia. The pus was entirely extracapsular and came from the ilium through a small opening just above the acetabulum. The cortex of bone was removed by means of an osteotome, and the bone was eburnated. A cavity filled with pus was exposed. This cavity led into two deeper cavities filled with pus. These cavities were saucerized, Carrel-Dakin tubes inserted, and the wound left wide open for drainage. Bacteriologic examination showed Staphylococcus aureus. The pathologic report was "purulent osteomyelitis without tubercles."

The patient's convalescence was uneventful; the wound remained clean, healed rapidly, and the symptoms in the hip disappeared completely. He was discharged from the hospital with a nonweight-bearing caliper on April 27.

On Feb. 8, 1929, at the time of the last observation, the patient had been free from all symptoms, had gained 20 pounds (9 Kg.) and his general health was excellent. There was a small pinpoint sinus in the scar, from which there was no drainage.

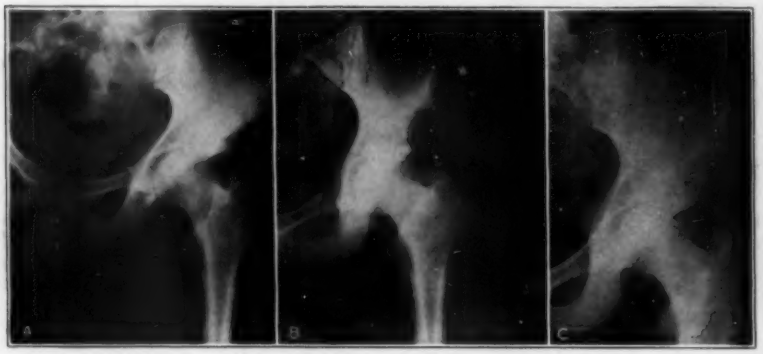

Fig. 7 (case 3).—*A*, roentgenogram showing localized abscess in the periacetabular region not involving the hip joint. *B*, roentgenogram made after operation. Saucerization of the abscesses was done without involving the acetabulum. *C*, roentgenogram taken after clinical cure was obtained. Note the apparent bone obliteration of the cavities.

Case 4.—C. E., aged 15, entered the University of Michigan Hospital on Nov. 23, 1923, with chronic suppuration, marked deformities of both hips and draining sinuses. The onset was a year previous to admission. There was pain in the left hip and anterior aspect of the thigh. The patient had a high fever, was acutely ill and was kept in bed. On December 3, he was sent to a hospital at Lansing, Michigan, where a diagnosis of "typhoid fever" was made. He was in the hospital six weeks, swelling in the hips, knees and the ankles developing; the left shoulder became sore, and the left hip assumed a flexion, abduction and external rotation deformity. The right hip was in a position of adduction, flexion and internal rotation. Six months after onset an abscess in Scarpa's triangle developed on the left side, which ruptured spontaneously and which has drained ever since. A few weeks later a similar abscess developed on the right thigh and ruptured; it was still draining on the patient's admission to the University Hospital.

Physical examination showed an anemic scrawny child. A hard mass was felt in both lower abdominal quadrants in the region of the internal iliac fossa. This mass was not fluctuant. There were iliac abscesses. The left shoulder was limited in abduction especially, but in all motions somewhat. The right hip was held in abduction, flexion and internal rotation. There was a flexion contracture of the knee. There was marked limitation of motion of the hip in all directions. The left hip was ankylosed solidly in abduction, flexion and external rotation. There was a flexion contracture of the left knee.

The patient was given fluids and two transfusions.

On Dec. 18, 1923, operation was performed, and the abscesses in left Scarpa's triangle incised and drained. On Jan. 12, 1924, the right anterior abscess was drained. On January 15, the left sacro-iliac joint was drained by Smith-Petersen's approach.

Roentgenograms showed pathologic dislocation of the right hip with absence of the head. The left hip showed bony ankylosis.

The patient's general condition was not good at any time, and it was felt that he would not stand extensive operation until he could be put in better physical condition. He showed clinical evidence of amyloidosis. The urine contained hyaline and granular casts, 200 white blood cells, many cocci and a few bacilli. Numerous transfusions were given and incision and drainage of the abscesses performed several times.

On July 3, the patient appeared in fair condition for him, so an attempt at resection of the ilium was made. The incision under the crest was used; the ilium was exposed and found to be filled with abscesses. The outer table was removed and Carrel-Dakin's tubes inserted.

On August 17, the patient died of symptoms corresponding to those of brain abscess.

CASE 5.—C. H., aged 14, entered University of Michigan Hospital on May 13, 1924. The onset of his condition was the year previous with pain in the right hip, which was severe, confining him to bed. A week later the leg was in flexion deformity. The patient was taken to a hospital, where he remained for seven months. The right hip discharged spontaneously, and there had been a discharging sinus there since. Two months before admission, the opposite hip became painful and finally opened spontaneously, leaving a discharging sinus.

Physical examination showed the right hip in a position of marked external rotation and abduction, and the left hip in a position of adduction and flexion, with limitation of motion. There were no areas of tenderness over the femoral shaft. There was a sinus in the posterior aspect of the left thigh and two sinuses in the upper third of the femur. The right hip was ankylosed in a position of 60 degrees abduction and 15 degrees flexion.

The diagnosis was pathologic dislocation of the left hip, osteomyelitis of the trochanter and upper third of the left femur and osteomyelitis of the right wing of the ilium with extensive involvement of the acetabulum.

On May 17, the ilium was incised and drained, and numerous small sequestrums were removed. Bacteriologic examination showed staphylococcus with slight hemolytic tendencies.

On June 7, saucerization was done.

On June 21, saucerization of the femur was done followed by dislocation that afternoon. Dislocation occurred after this operation for osteomyelitis of the trochanter, very probably influenced in part by loss of the gluteus muscles and abduction of the opposite leg.

On December 3, Steinman pin traction was used to pull the left leg down for reduction of the dislocated hip.

On December 20, the pin was removed because of infection.

On Aug. 5, 1926, the wounds were practically healed. The patient was in good enough condition so that osteotomy could be considered to correct the deformity of the right hip.

On September 8, the patient returned to the hospital with an abscess, which was drained.

On March 3, 1927, an abscess over the right trochanter was incised and drained.

On April 1, the patient returned with a temperature of 101.8 F., pulse rate 90, respirations 22, a flare-up in the right lower quadrant just above the anterior superior spine and an abscess in the lower lumbar region. At this time the urine showed albumin 4 +, casts and white blood cells. There were 40,000 leukocytes.

On April 4, an abscess in the lumbar region was incised and drained.

On Feb. 21, 1928, osteotomy was done to correct the deformity of the right hip.

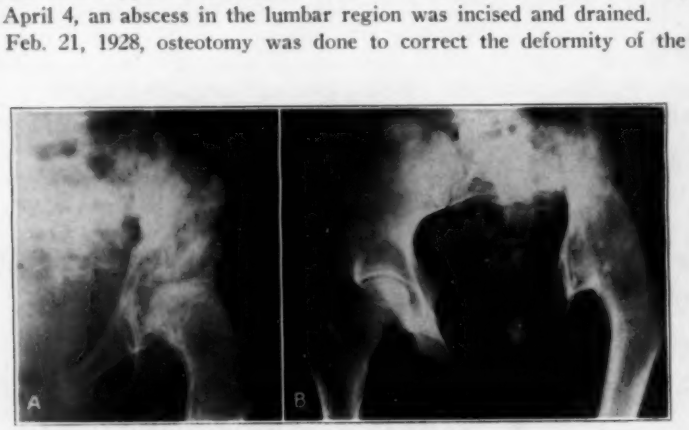

Fig. 8 (case 6).—*A*, roentgenogram showing subacute osteomyelitis of the ilium of the diffuse type with invasion of the hip joint. Note the mottling with areas of increased density intermingled with rarefied areas. *B*, roentgenogram taken after operation; partial resection and excision of the outer table was done. Numerous sequestrums were found in the supra-acetabular portions of the body of the ilium.

On April 4, suppurative parotitis developed.

Death occurred on April 8 from pyemia.

CASE 6.—L. L., aged 13, entered the University of Michigan Hospital on Oct. 6, 1924. The condition began with a painful left hip on September 4, following a severe cold. On October 8, incision and drainage was performed and was repeated on November 5, November 20, April 23, 1925, June 19, and September 15. On September 22, incision and drainage of the clavicle was performed; on May 19, 1926, incision and drainage of an abscess of the cheek; on July 9, incision and drainage of an abscess in the left axilla and right thigh, on December 24, incision and drainage of the right humerus and on Nov. 5, 1927, incision and drainage.

On December 2, iliectomy was performed, the usual incision being used. There was a large abscess between the iliacus and internal table, penetrating the iliacus fibers. There were two large sequestrums in the abscess and a hole in the anterior portion of the ilium communicating with the abscess. The abscess also followed the sinus tract under the ilium to point at the sciatic notch. Iliectomy was per-

formed, the incision following the crest of the ilium, and the ilium was explored subperiostially, stripping the gluteal and abdominal muscles from the crest. The ilium was removed almost to the pubic ramus. A sinus which communicated with the abscess in the iliacus muscle was found just below the sciatic notch.

The pathologic examination showed chronic purulent osteomyelitis.

On July 11, 1929, the patient returned with an abscess over the posterior end of the scar over the left ilium. The abscess was healing satisfactorily.

In January, 1931, when the patient was last seen, she had had no further recurrence of the difficulty in the ilium. However, she returned to the hospital in January, 1930, with a recurrence of osteomyelitis in the clavicle.

CASE 7.—D. D., aged 23, entered the University of Michigan Hospital on Dec. 30, 1926, with history of an acute osteomyelitis of the left tibia at 15 years of age. While the patient was on a geological survey in California a month before entrance to the hospital, a severe pain referred to the left sacro-iliac joint developed. He was treated in a hospital in California for acute sacro-iliac strain. After four weeks he was becoming progressively worse, so entered the University

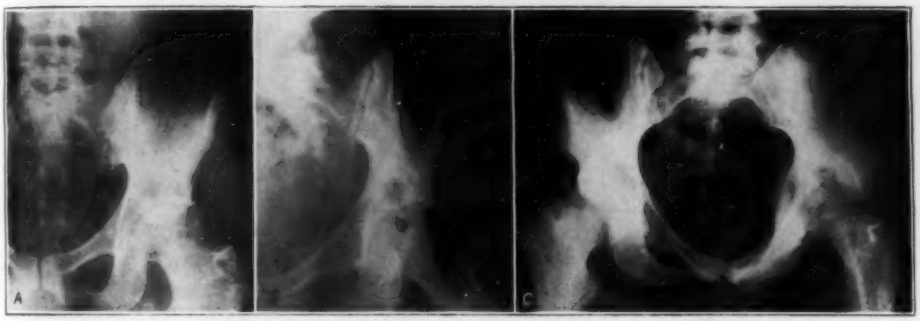

Fig. 9 (case 7).—*A*, roentgenogram showing a rarefied area in the ilium above the acetabulum but not invading the hip. The patient was operated on elsewhere by trephine. *B* shows apparent perforation into the acetabulum; osteoporosis of the head of the femur and narrowing of the joint cavity. *C* shows more marked evidence of involvement of the hip. The rarefied area is still prominent and not tending to close by bone proliferation.

Hospital at Ann Arbor. At the time of admission there was a large fluctuating abscess pointing just below Poupart's ligament medial to the anterior superior spine of the ilium. There was marked limitation of motion of the left hip associated with muscle spasm. A flexion contracture was present. The hip, on gentle movements, could be moved fairly freely. The patient was acutely ill and had a temperature of 100.6 F.; pulse rate, 120; respirations, 24, and leukocytosis.

A roentgenogram showed an area the size of a nickel in the ilium just above the acetabulum but not perforating it, which seemed to be the focus of the difficulty. A diagnosis of osteomyelitis of the ilium was made. My intentions at first were to drain the anterior abscess and then drain the ilium by a trephine operation, but the patient was too toxic for an extensive operation.

The abscess, which was very extensive, was drained through an incision over the crest of the ilium anteriorly on the visceral side of the ilium. The internal table of the ilium was felt with the fingers, and no perforation could be found. It was thought wise to stop at this point. Following the operation, the infection in the

hip joint subsided completely, but the patient had symptoms of sciatic irritation with hyperesthesia of the left great toe. Repeated roentgenograms showed the suspicious rarefied area in the ilium filling in with lime salts. The patient recovered completely.

He returned in January, 1927, with another large abscess in the internal iliac fossa. The ilium still looked normal. The abscess was drained anteriorly, and extensive exploration of the visceral side of the ilium showed no definite site of the infection. Staphylococcus aureus and albus were found.

On May 8, 1928, a third iliac abscess formed and was drained. This time the anterior border of the ilium was dissected free subperiostially, and an excellent view of the entire internal table of the ilium showed no evidence of perforation or active involvement. The sacro-iliac joint appeared normal roentgenographically and clinically.

The patient was free from symptoms following this until 1929, when he was injured in California and pain again developed in the left hip. He was treated by one of the leading orthopedists there. The previously described area of decreased density was noted in the ilium, a trephine operation was performed, and a cavity containing pus was found. Following this operation the wound healed, but a fibrous ankylosis of the hip resulted. There has been no flare-up of the infection since.

Case 8.—M. R., aged 17, entered the University of Michigan Hospital on July 8, 1927. He dated December, 1924, as the time of onset of his condition. The primary trouble was in the right tibia, later in the femur, and in 1926 the left ilium became involved. The patient gave a history of chills, fever, redness and tenderness over the right tibia, and pain in both knees.

There was marked tenderness over the crest of the ilium with a discharging sinus at the crest of the left ilium.

Roentgen examination showed a defect of the ilium on the left side in the region of the superior iliac spine.

On September 26, an incision 5 inches (12.7 cm.) long was made along the crest of the left ilium from the anterior superior spine posteriorly. An abscess cavity was found which centered around a perforated hole in the ring of the ilium, the hole being 3 cm. in diameter. The crest above this was removed, the scar tissue excised, and the wound loosely closed. The femur and tibia were also drained.

In January, 1929, the patient reported back to the hospital. The ilium was completely healed.

The pathologic report showed active purulent osteomyelitis.

Case 9.—P. S., a youth, aged 18, was admitted to the University of Michigan Hospital on Feb. 8, 1929, with a condition which began three years previous to admission, the result of a misstep. His right foot doubled up under him, and difficulty in walking followed. Four days later he had an elevated temperature, and the doctor diagnosed typhoid fever, but the chief complaint was in the right hip. The patient was in bed six months, following which he got around but he had pain in the right hip, and the leg became shorter. One year before admission a sinus developed over the anterior aspect of the hip, and this had drained since its appearance.

Physical examination showed no motion in the right hip, and it was ankylosed in a position of 40 degrees adduction and 60 degrees flexion. There was no pain. There was a draining sinus on the anterior aspect of the joint. There was ½ inch (1.27 cm.) true shortening and 4 inches (10.16 cm.) apparent shortening.

On February 14, operation was performed. From four to five perforating holes were found in the wing of the ilium with tissue formation extending through to the iliacus; one large cavity led directly to the iliacus and drained into a sinus in the groin. The ilium was removed from just above the pubis to the posterior one-third.

On March 6, secondary closure was done.

Pathologic examination showed purulent osteomyelitis, very active osteomyelitis with marked necrosis of the bone and many foreign giant cells.

On June 3, the patient returned with excellent results except for two small sinuses at the center of the wound, the rest being healed. There was definite regeneration of tissue.

On November 16, there was complete healing.

CASE 10.—E. D., aged 17, was admitted to the University of Michigan Hospital, on Aug. 8, 1927. On January 1, the right ankle was slightly reddened and swollen. Two weeks later there was swelling of the right knee and pain in the right hip on

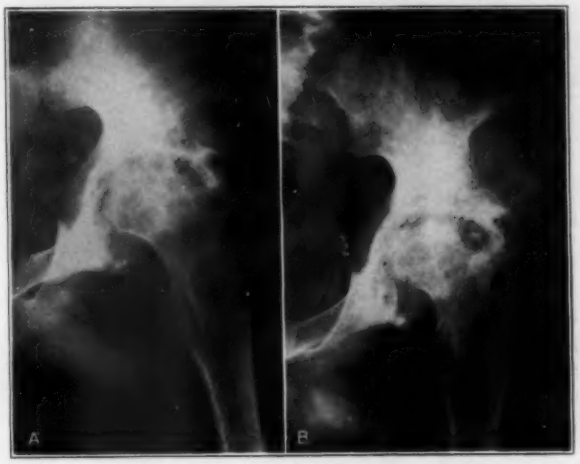

Fig. 10 (case 10).—*A*, roentgenogram showing involvement chiefly about the acetabulum and anterior third of the ilium with partial ankylosis of the hip. *B*, roentgenogram taken some months after operation. Note area of resection with regeneration of bone.

walking, associated with chills and fever. The patient was in bed for two months, and there was a loss of weight of 30 pounds (13.6 Kg.). The patient entered the hospital walking with a cane, complaining of pain in the knee.

The right hip was held in 35 degrees flexion deformity, neutral in position, and 1 inch shortening. The trochanter was 1 inch above Nelaton's line, with some atrophy; there was ankylosis of the hip, and the knee was normal.

The roentgenograms showed a destructive process which had destroyed the head of the femur and corresponding surface of the acetabulum. The process had extended well into the ilium.

Operation was performed on August 25. There was a large involucrum formation lateral to the anterior superior spine of the ilium in which there was a large amount of pus and a few partially separated sequestrums. The involucrum was removed, as was the outer cortex of the ilium down to the acetabulum. Saucerization of the outer cortex of the ilium was performed.

The pathologic report was active chronic purulent osteomyelitis. The bacteriologic report showed Staphylococcus aureus.

In November the patient had some pain in the right thigh on motion, but by December 30 he was free from symptoms. There was no tenderness over the pelvis or femur, and there were no sinuses.

CASE 11.—J. M., aged 14, entered the University of Michigan Hospital on July 30, 1927. One year before admission, he had fallen from a tree; since then he had had pain in the right hip. The day before admission pain and swelling developed in the left elbow.

Physical examination showed a sinus in the anterolateral surface of the right femur with marked muscle spasm and fixation of the hip joint in abduction, flexion and external rotation. Movements could be carried through almost normal range if carefully done. There was swelling over the ilium with marked thick-

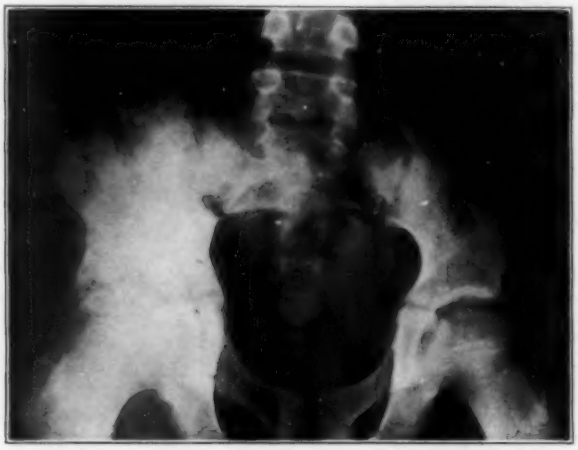

Fig. 11 (case 11).—Roentgenogram showing typical chronic diffuse osteomyelitis of the ilium. Note the tremendous bone proliferation and the areas of marked density with rarefied areas spread throughout. The sacro-iliac joint also is involved. Resection is indicated in this type of case though the external table was excised.

ening of the bone. The left elbow showed synovial thickening, increased fluid, tenderness and limitation of motion.

On September 27, operation was performed on the right ilium, the external table being exposed only by incision under the crest of the ilium and subperiosteal resection. This was somewhat difficult because of dense marked involucrum formation extending in knobs well away from the ilium proper. There were many abscesses throughout the bone and an abscess in the soft tissue just above the acetabulum. The anterior third of the outer table with the involucrum was removed, and the wound was treated with Carrel-Dakin technic. The hip cleared up quickly, all symptoms disappearing, and the elbow improved completely simply by aspiration.

On July 19, 1928, a sinus persisted over the ilium, and a recent flare-up brought the boy back to the hospital. The ilium was explored subperiosteally by incision under the crest. The outer table had reformed with dense involucrum and numerous

abscess cavities throughout. In the posterior third of the ilium between the two cortical layers a large pus cavity was found containing several small sequestrums. No abscesses pointing toward the visceral side could be seen. Bone was removed almost to the internal table of the ilium.

On April 9, 1929, the patient returned to the hospital and at this time the hip was entirely normal. There was a slightly draining sinus over the inguinal region, which was symptomless.

CASE 12.—F. L., aged 16, was admitted to the University of Michigan Hospital on March 30, 1929. A diagnosis of chronic osteomyelitis of the right hip and ilium, pathologic dislocation of the right hip and acute thrombophlebitis of the left leg was made. The onset was three years prior to admission, the patient having been injured while playing football. There was pain in the hip, and the patient walked with a limp. In May, 1928, he had a high fever and severe pain in both hips. In September, 1928, a sinus appeared in the right thigh, and in December, 1928, there was drainage of the right hip.

Physical examination showed an acutely ill, markedly emaciated patient with decubitus over the back, scapula, sacrum and calf of the left leg. The right elbow was slightly fixed. There was a long scar over the right thigh with a draining sinus at the lower end from which greenish-yellow purulent pus flowed. There were marked limitation of motion of the hips in all directions, definite fluctuation in the thigh and 1 inch (2.5 cm.) shortening of the right leg.

A roentgenogram showed a marked destructive process including the head and neck of the right femur and the right ilium, dislocation of the head of the femur and sacro-iliac synchondrosis involvement on the right.

On May 23, incision and drainage of the iliac abscess was performed by Dr. Hart. The abscess occupied the right iliac fossa beneath the iliac muscle. The wound was packed. Iliectomy was advised later.

On June 1, the wing of the ilium was removed from the anterior superior spine to the sacro-iliac synchondrosis behind.

Pathologic examination revealed very active chronic purulent osteomyelitis.

At the last report the abscess had healed.

CASE 13.—H. E., aged 18, entered the University of Michigan Hospital on Aug. 20, 1928. At the age of 7 the patient fell and dislocated the left hip. Pain continued for a year, and limping resulted. Operation was performed elsewhere a year before admission, and two draining sinuses were present on admission.

Physical examination showed the hip held in a position of 35 degrees adduction, 35 degrees flexion and slight internal rotation. There was apparent shortening of 3 inches (7.6 cm.) and the actual shortening was 1½ inches (3.8 cm.). There was a limitation of motion of about 10 degrees forward and lateral, and about 20 degrees internal rotation. Urinalysis at that time showed albumin 1+, hemoglobin 76 per cent and leukocytes 23,000.

Iliectomy was performed on Sept. 4, 1929, by Dr. Hart. The wing of the ilium was excised. There was marked thickening, several small perforations on the visceral side and no subiliac abscesses.

Pathologic examination showed pyogenic granulation tissue containing necrotic bone, chronic osteomyelitis and osteitis. Bacteriologic culture revealed B. coli.

On October 12, there was secondary closure.

The last report showed that the wound was healed and the patient apparently was cured.

CASE 14.—C. H., aged 16, entered the University of Michigan Hospital on May 7, 1928; two years before entrance an attack of pain and swelling in the left

hip and spine developed; he was placed in a spica and kept in bed for two months. He has no remembrance of fever. The pain subsided, the cast was removed, and the patient was symptomless until three months before admission. At that time a sinus which has since drained developed. At no time were there pain, swelling or fever, and there were no symptoms in the hip.

Physical examination showed a draining sinus in the region of the left sacro-iliac joint and thickening of the ilium posteriorly, but no evidence of involvement of the hip.

A roentgenogram showed sequestration in a perforated cavity in the ilium. The sacro-iliac joint appeared involved with sclerosis.

Operation was performed on June 7. Incision was made over the posterior two thirds of the crest of the ilium to the posterior superior spine and continued down the trochanter. The gluteal muscles were separated from the crest of the ilium down to the junction of the inferior spine and sacrum. Incision was then carried through the gluteus maximus. A sequestrum was found lodged in the sinus, and this was removed. The sinus tract could not be traced to the ilium, and the exposed portion of the ilium and outer cortex appeared normal. A window was

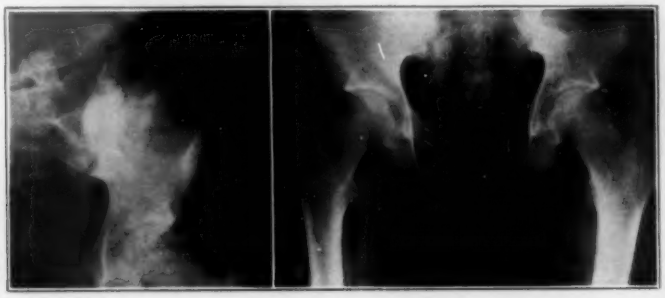

Fig. 12 (case 14).—Roentgenograms showing involvement of the posterior third of the ilium with invasion into the sacro-iliac joint.

cut out of the ilium to the sacro-iliac joint and a very thick cartilage found. There was no pus. The window was removed and a small drain inserted.

Pathologic examination of a specimen of necrotic hyaline cartilage showed no actual infection.

A roentgenogram on Sept. 11, 1929, showed an operative defect in the left wing of the ilium, increased calcification and involvement of the left sacro-iliac joint, but no evidence of activity.

On February 23, the patient returned with a draining sinus. A roentgenogram showed extension of the process in the ilium.

On March 1, iliectomy was performed. Incision was made along the crest of the ilium and posterior two-thirds carried through the gluteus maximus fibers to the trochanter. The ilium was exposed, and a large opening found in the posterior lower portion just in front of the greater sciatic notch. This was filled with pus and granulation tissue, and several sequestrums of large size were removed from this opening. The epiphysis of the crest was dissected free with the abdominal muscle insertions, and the inner table of the ilium was exposed. With an osteotome, the wing of the ilium was removed, exposing a large abscess cavity in the inner table, which had broken through and led between the periosteum and inner table of the ilium. The cavity in the ilium itself was ¾ inch (1.9 cm.)

long and ½ inch (1.27 cm.) wide. The ilium was removed from the posterior one-third to the sacro-iliac joint. This joint was opened. It showed no pus, but there was definite thickening and fibrosis.

On March 22, secondary closure of the wound was done. Bacteriologic examination showed Staphylococcus aureus. Pathologic examination showed degenerating cartilage, pyogenic granulation tissue, numerous foreign body giant cells and very active chronic purulent osteomyelitis.

The last report, made on September 10, showed that there had been a history of draining sinus since the patient left the hospital. At one time a small sequestrum was removed. There was one attack of high temperature, breaking down of the wound, and extensive drainage of pus followed by complete relief. The patient was apparently cured.

Case 15.—L. S., a woman, aged 29, entered the University of Michigan Hospital in August, 1926. The onset was six months before entrance to the hospital. There was swelling over the posterior aspect of the thigh and pain on walking. Incision and drainage were employed elsewhere, and the patient was confined to bed for ten weeks. Following this, there had been a discharging sinus with occasional spicules of bone.

Physical examination showed a sinus in the posterior aspect of the thigh above the greater trochanter. The hip was normal clinically.

Operation was performed on August 30, by Dr. Hensel. There was a destructive osteomyelitis with attempted repair, involving the upper third of the anterior two thirds of the ilium with multiple abscess formation and involucrum in the bone. The ilium was about 2 inches (5 cm.) thick at the crest. Both tables of the ilium were exposed by subperiosteal reflection, and the diseased area was completely resected. The wound was kept open, and Carrel-Dakin treatment was instituted.

In January, 1927, the wound was reported completely healed and the patient apparently cured.

Case 16.—E. N., a man, aged 70, entered the University of Michigan Hospital on Feb. 17, 1926. He had previously received a penetrating wound over the right ilium while cutting a board with a circular saw. The wound never quite healed, and a draining sinus had persisted.

Physical examination showed a discharging sinus over the lateral surface of the right ilium. There were slight limitation of motion and pain in the right hip.

A roentgenogram showed a perforation of the ilium 1 inch above the acetabulum about 1½ inches in diameter.

Operation was performed on April 26, by Dr. Visick. An incision parallel to the gluteal fibers led directly to a large abscess cavity in the wing of the ilium, filled with granulation tissue, pus and a small sequestrum. A large piece of wood, 1½ inches in length and 1 inch in width, was removed. The cavity was curetted. The wound was kept open and treated by Carrel-Dakin technic.

In December, 1927, the patient returned with the wound completely healed.

Case 17.—M. B., a woman, aged 21, entered the University of Michigan Hospital on Feb. 23, 1927. Two and a half years before admission, pain on walking developed in the hip. An abscess formed, which was drained by the home physician, and the patient was confined to bed for three months. There had been a persistent sinus, and she had had four subsequent similar attacks of pain followed by an abscess which drained spontaneously.

Physical examination showed a small draining sinus in the left inguinal region near the anterior spine apparently from an internal iliac fossa abscess. The hip joint was normal.

A roentgenogram showed an irregular area of bone absorption in the wing of the left ilium posterior to the anterior superior spine with osteosclerosis surrounding it.

Operation was performed on March 5, by Dr. Darling. An incision was made over the crest of the left ilium, and the ilium was explored by subperiosteal reflection. A sequestrum, 1.5 cm. in diameter, was removed from between the tables of the ilium. Saucerization of the cavity was done. The pathologic report showed pyogenic granulation tissue, active purulent inflammation and fragments of necrotic bone. In one portion granulation tissue showed many tubercles.

A diagnosis of pyogenic and tuberculous infection was made.

On July 7, 1927, the patient reported back to the hospital with the abscess completely healed and apparently cured.

Case 18.—J. H., a youth, aged 16, entered the University of Michigan Hospital in April, 1929. There had been an injury to the right hip in November, 1918. Three weeks later an acute respiratory infection developed and was followed a week later by severe painful swelling in the right hip. The patient's temperature

Fig. 13.—Photograph of a partial resection to demonstrate the areas of perforation commonly seen in osteomyelitis of the ilium.

was 104 F., and he had chills. A little later osteomyelitis of the left tibia and humerus developed. Eight weeks later he was taken to a reputable clinic where a diagnosis of tuberculosis was made. He was advised as to heliotherapy and antituberculous regimen.

Physical examination showed the right hip held in flexion and slight adduction, and there was marked local tenderness over the right ilium. An indurated tender mass could be palpated in the right lower quadrant. There were ¾ inch (1.9 cm.) actual shortening and 1¼ inches (3.1 cm.) apparent shortening of the right leg. There were marked limitation of motion of the right hip and almost a complete fibrous ankylosis; osteomyelitis of the tibia and humerus was also present.

Operation on the ilium was performed on May 8, a subperiosteal exposure of both tables being used. The ilium was markedly thickened with numerous superficial abscesses in the outer table. The inner table had two perforations with internal iliac abscesses filled with necrotic bone and pus. The wing of the ilium was resected from the upper margin of the hip joint. The wound was packed open.

On June 10, a secondary closure was performed.

On October 21, the patient returned to the hospital in excellent general health, walking with crutches. There was a slight draining sinus over the ilium.

CASE 19.—J. L., a youth, aged 20, entered the University of Michigan Hospital in October, 1924. The onset was eight years before admission. The patient injured his hip while skating, and the following day pain in the abdomen and left hip developed, with high fever and delirium for two or three weeks. This was diagnosed "typhoid fever." An abscess pointed in the left groin and ruptured spontaneously. Several other sinuses appeared. There has been chronic suppuration for the past eight years.

Fig. 14.—Roentgenogram showing chronic osteomyelitis of the ilium of twenty-five years' duration. Note the bony ankylosis of both the hip and the sacro-iliac joint, also the density of the body of the ilium. Several very extensive abscess cavities with pus under pressure were found here. Chronic diffuse osteomyelitis of the ilium.

Physical examination showed a sinus over the sacro-iliac joint posteriorly and another draining sinus distal and medial to the anterior superior spine of the ilium. The hip was ankylosed in adduction, flexion and external rotation.

Operation was performed on October 29. A lateral incision was made through the gluteus medius fibers, the anterior half of the ilium being exposed. A large perforation through both wings of the ilium which connected directly with an abscess in the internal iliac fossa was found. Curettement was done, and Carrel-Dakin treatment was instituted. The wound did not heal, and discharge continued.

Another operation was performed on Jan. 31, 1925. The ilium was exposed subperiosteally by an incision beneath the crest and stripping of the periosteum off both tables. An abscess in the internal iliac fossa had been insufficiently drained at the previous operation through the spontaneous perforation. The sartorius muscle and Poupart's ligament were dissected free from the anterior spine of the ilium. The anterior two thirds of the ilium from a point above the acetabulum was resected. This gave an excellent exposure of the greatly thickened ilium posteriorly. Between the two tables numerous sequestrums which extended back almost to the sacro-iliac joint were found. The sequestrums and the outer

Fig. 15.—A schematic drawing illustrating the incision employed and emphasizing how prominently the ilium protrudes through the wound after subperiosteal resection of the muscles. In this type of case resection of the wing is done. Poupart's ligament can be reflected also from the spine of the ilium and one may remove the bone from the superior ramus of the pubis back to the sacro-iliac joint. The approach is termed Larghi's by Bergmann.

table were removed. The wound was left wide open, and Carrel-Dakin treatment was employed.

In February, 1929, when the patient was last seen four years after operation, he reported that he had had no difficulty since six months after operation and had been working daily. The hip fixed in 80 degrees flexion and 10 degrees adduction, not a bad position for function. He had been walking with a lift on his shoe. Osteotomy was advised but refused.

CASE 20.—F. A. S., a man, aged 43, entered the University of Michigan Hospital on July 18, 1924. The onset of his condition was three years before admission. He had his appendix removed. A year before admission an abscess developed and this was drained in October. The abscess was apparently pelvic in nature, pointing in the inguinal region. It drained for six weeks, and the sinus had not healed since drainage.

Physical examination showed a discharging sinus in the right iliac region just below the crest of the ilium at the outer edge of the inguinal ligament. There were limitation of motion of the hip and pain on motion.

A roentgenogram on July 21 showed bone necrosis in the upper portion of the right ilium. There were no sequestrums. There was a bone defect in the upper portion of the right ilium of considerable size, the lower end of which was greatly thickened.

Operation was performed on June 8, 1925. A triangular area was removed from the ilium. The process appeared to extend below the area removed and seemed to be sclerotic bone.

On April 8, 1926, the sinus was almost healed. Respiratory infection contraindicated radical surgical procedures at that time. The patient was requested to return for extensive operation in case the sinus did not remain healed.

CASE 21.—N. L., a man, aged 31, entered the University of Michigan Hospital on Jan. 7, 1926; he had pain in the right hip and abdomen and a sinus in the anterior part of the hip. The onset was five years before entrance following a gunshot wound. Operation for removal of the bullet was performed in May, 1920. The patient had had pain in the hip since that time. Two other operations were performed for incision and drainage of the abscess.

Physical examination showed an abscess on the left side of the second and third lumbar vertebrae. The hip joint was freely movable but painful. There were 4 inches (10.16 cm.) apparent shortening and 3 inches (7.6 cm.) true shortening. Abduction was limited, and there was some atrophy of the right leg. There were numerous operative scars on the right buttock and hip and a sinus in the anterior portion of the groin.

Operation was performed on January 15. The sacro-iliac joint was exposed. Gross appearance of the joint was that of infection, but no frank pus was seen.

The pathologic report showed chronic osteomyelitis.

On March 30, a second operation was performed. A rectangular section of the entire thickness of the ilium was removed, and a chronic abscess of the mesial side of the ilium embedded in the iliacus muscle was drained. The patient had a prolonged convalescence with a discharging sinus for months following operation.

On April 19, 1927, the patient returned to the hospital with the wounds entirely healed. Movement in the hip was slightly limited, especially abduction. There was 3 inches shortening of the leg.

CASE 22.—This case is reported by the courtesy of Dr. James R. Tillotson, Lima, Ohio. Roentgenograms were seen and resection or removal of the outer table advised by Dr. Badgley in January, 1928.

V. M. S., a girl, aged 12, had had a chill on July 29, 1927, followed by high temperature which continued over a period of two weeks. There was considerable swelling in the right hip extending down to the knee. There was severe pain in the hip. The local physician made a diagnosis of "muscular rheumatism." Heat was applied, and the patient was confined to bed until September 11. She was up part of the time in September and was confined to bed again in October. She was up about three weeks in November, became worse, and was again confined to bed. Dr. Tillotson and Dr. Martin were called in for consultation in August, 1927. At that time there was swelling about the hip but no redness. There was acute pain

in the hip, and the patient had a fever. On Jan. 6, 1928, she was admitted to the Lima City Hospital under the care of Dr. Tillotson.

Roentgenograms taken on Aug. 13, 1927, showed some rarefaction of the ilium, especially about the right acetabulum, and also some rarefaction at the symphysis pubis. The flat portion of the ilium showed little or no change.

Roentgenograms in October, 1927, showed the entire ilium porous, also the ramus of the pubis; at the symphysis it looks as if it were about to separate from the opposite side. There was breaking through of the periosteum in several places.

Roentgenograms in November, 1927, showed no progress of the disease.

Roentgenograms on Jan. 11, 1928, showed a marked osteoporosis of the entire right ilium. The pubis appeared about the same as before. At that time both Wassermann and Pirquet tests were negative.

The diagnosis was osteomyelitis.

Operation was performed on February 28, the Smith-Petersen incision and subperiosteal dissection from the crest of the ilium to the acetabulum being used. The outer table of bone was removed, 3 by 4 inches. It was drained anteriorly, and an abscess in the mesial aspect of the right thigh in the upper third was incised.

The patient was discharged from the hospital on May 6. There was no drainage. At this time patient was walking, and there was no impairment of motion.

At operation there was seen a honeycomb condition of bone with pockets of pus, staphylococcus and pneumococcus.

Case 23.—J. N., a man, aged 22, entered the University of Michigan Hospital on April 18, 1928. At the age of 16, following a fall on the right hip, there was sudden onset of the condition. There were pain and limitation of motion in the hip, high temperature and abscess formation with incision and drainage, followed by persistent sinuses. The patient was hospitalized for eighteen months. Since that time he had had an ankylosed hip in position of marked abduction, external rotation and flexion.

Physical examination showed the hip ankylosed in external rotation, 45 degrees abduction and 30 degrees flexion. There was a draining sinus posterior to the right sacro-iliac joint and numerous healed scars over both the right and left hips. Urinalysis at this time showed albumin 4 + with many red and white blood cells.

The roentgenograms showed bony ankylosis of the hip in the deformity noted. There were marked thickening of the upper portion of the ilium and evidence of bony proliferation. There was an area of rarefaction with a shadow of increased density in this area suggesting a sequestrum.

Operation was performed on April 21. The ilium was exposed by subperiosteal reflection on the mesial and external sides. A large abscess cavity on the mesial side of the ilium which was in the substance of the iliacus muscle and extended down deeply below the pubic ramus was explored. Several areas of perforation were found in the wing of the ilium. The wing of the ilium from the anterior superior spine to the sacro-iliac joint was removed to just above the acetabulum. Several small sequestrums were found in the cavities in the ilium.

The bacteriologic report showed Staphylococcus aureus.

The patient returned on December 27, and at that time general condition was excellent.

Case 24.—F. G., a woman, aged 35, entered the Henry Ford Hospital in March, 1929. The onset of her condition was at the age of 10 years with "typhoid fever." The patient was acutely ill with pain in the left hip. The hip assumed the deformity of abduction, external rotation and flexion, which was corrected by a plaster spica. The patient was confined to bed for weeks. After the spica was

removed, the hip was ankylosed. In 1907, a "curettement" of the ilium was done. In 1920, the flexion contracture of the hip was corrected by an osteotomy. In 1928, an abscess developed over the left hip and drained spontaneously. Six months before admission pain in the left hip and a sinus in the left labium developed.

Physical examination showed healed operative scar over the left ilium with loss of normal contour of the ilium. There was an old operative healed scar over the trochanter. There was a sinus in the left labium majora which on probing drained toward the pubis.

Roentgenograms showed evidence of partial resection of the crest of the ilium, marked thickening and sclerosis of the remaining portion with an area of decreased density above the acetabulum surrounded by eburnated bone, very probably abscess cavities. Both the sacro-iliac and the hip joint showed bony ankylosis. Injection into the sinus of iodized poppy seed oil 40 per cent led to the femur where there was an old osteomyelitis.

Operation was performed on March 18. Subperiosteal reflection of the external table of the ilium was performed. Dense eburnated bone was exposed throughout the wing of the ilium to the acetabulum, and thick cortical bone and involucrum were removed. After about an inch in thickness had been removed, several large cavities filled with pus were exposed under pressure just above the acetabulum and extended back toward the sacro-iliac joint. No sequestrums were found. Resection was not done as saucerization seemed complete.

The bacteriologic report showed Staphylococcus aureus.

In May, 1930, the patient reported back in excellent health. The sinus in the labium majora was healed. There was a slightly discharging sinus over the outer aspect of the ilium.

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PANCREATIC TISSUE IN THE WALL OF THE STOMACH

E. S. J. KING, M.S., F.R.C.S.
Surgeon to Outpatients, Melbourne Hospital

AND

P. MacCALLUM, M.C., M.A., M.Sc.
Professor of Pathology, University of Melbourne

MELBOURNE, AUSTRALIA

Nodules of tissue indistinguishable microscopically from pancreas have been observed by many investigators and have been discussed at length, deservedly, in numerous papers. Not only is such a phenomenon of considerable interest, but it presents a fundamental pathologic problem. In many of the papers that have appeared, not only have hypotheses which are untenable in the present state of knowledge been proposed, but even patently inaccurate observations have been made. In addition, certain relevant features of considerable import in the determination of the nature of these masses have been overlooked.

HISTORICAL DATA

The earliest record of the occurrence of pancreatic tissue in the stomach which is available to us is that of Zenker, published in 1861. He referred to a previous note by Klob in 1859, and to some observations in lower animals by Leydig (1857).

Wagner (1862) and Gegenbauer (1863) reported other cases, and a few further reports appeared, until at the beginning of this century much interest was manifested in the condition. Thorel (1903) described seven cases of "aberrant pancreatic tissue," in three of which the tissue was in the stomach. In 1904, Warthin collected forty-seven similar cases from the literature, and in thirteen of these the aberrant tissue was in the stomach. He described one other case. Horgan, in 1921, collected thirty-two other cases, in five of which the condition was in the stomach. Beutler gave a good account of the literature.

Since then numerous accounts have appeared, some as special references to the occurrence of pancreatic tissue in the stomach, Delhougne, 1924; Griep, 1926; Hilarowicz, 1927; Münch, 1925; Vandendorp, 1928), and others in which the condition is merely referred to during a discussion on related subjects (Nicholson).

HYPOTHESES

The majority of the hypotheses of the origin of these tissues are closely interrelated.

Zenker suggested that they represent an anomaly occurring in early embryonic life in which an additional diverticulum arose from the duodenum. With growth of the tissues this supernumerary diverticulum became separated from the normal structure. Glinski postulated that one or more of the anlagen of pancreatic tissue failed to coalesce. Either of these hypotheses could explain only pancreatic tissue in the duodenal wall. Since the duodenum has been demarcated from the stomach at the time of budding of the pancreatic tissue, abnormalities of this bud cannot be carried into the contiguous parts of the intestine.

Warthin's view was that lateral budding of the rudimentary pancreatic ducts occurred as they penetrated the wall of the intestine. Since pancreatic tissue has been found in the cardia of the stomach and in Meckel's diverticulum, the budding must have proceeded with peculiar enthusiasm.

Horgan adopted an even more fanciful hypothesis. In describing the development of the pancreatic outgrowths, he said: ". . . branching buds come into contact with the wall of the stomach, intestine or mesentery and may become engrafted thereon." Such a view, apart from inherent improbabilities, does not adequately deal with tissue (*a*) on the anterior wall of the stomach, (*b*) in the submucous coat or, most particularly, (*c*) in Meckel's diverticulum, which lies anterior to the intestine, whereas the pancreatic bud, certainly the part referred to by Horgan, is mainly posterior.

PATHOLOGIC PRINCIPLES

In order to appreciate the difficulties which surround the subject and also to understand the reason for diverse opinions on some pathologic problems, it is necessary to consider the mode of development of pathologic thought.

It is axiomatic that pathology must conform with the fundamental sciences—biology and embryology. When pathology began to make rapid advances about seventy or eighty years ago, embryology was also advancing quickly. The principles laid down by the embryologists were accepted by pathologists and applied to pathologic processes. One such principle was that of the immutability of the germ layers. Another was the idea that the capabilities of cells for growth or further differentiation gradually diminished with differentiation. From this it followed that differentiated adult cells had lost all power of the formation of other tissues, and as a corollary of this, unusual tissue found in an organ must be derived from undifferentiated (or embryonic) cells.

From this principle was evolved Cohnheim's hypothesis of cell rests. When portions of tissue were found in an unusual situation, e. g., pancreatic tissue in the wall of the stomach, it was argued that since the adult cells had lost the potentialities of the original intestinal epithelium to give rise to various types of epithelia, this tissue must have arisen at a time when the cells of the intestine still retained a multipotential character, i. e., during embryonic life, or else certain of such embryonic cells remained latent within the limits of this hypothesis. The hypothesis of a "cell rest" with minor modifications is still strongly entrenched in pathologic thought and writings, in flagrant defiance of the principle that current pathologic opinion should advance with biology and embryology.

Cohnheim's hypothesis depends on embryologic views of eighty years ago. Has this science advanced since then and have any of its fundamental principles been altered? If so, then one must modify one's views in conformity with them. The failure of a great many modern pathologic investigations is caused by the fact that, so far as many investigations are concerned, pathology has become segregated from biology and to a less extent from embryology, and until rapport is established and a broad outlook adopted true advance must be retarded.

Recent investigations have shown that the potentialities of adult cells for proliferation and change into those of related but different type are not always lost, but are retained in varying degrees in different tissues. There is no doubt that accompanying progressive differentiation during development a certain inflexibility is imposed on cells. This corresponds with the fixation of morphologic attributes in certain parts of even the ovum, e. g., in some Coelenterata.

On the other hand, certain tissues retain, within certain limits, an extraordinary capacity for growth and alteration into tissue of a related type. Modern biologic and pathologic investigation is demonstrating the accuracy of this view. The reformation of synovial membrane (Key) and menisci (A. Gibson), the development of a new lens from the iris after removal of the original lens (Sato), the formation of the alimentary canal of insects from the epithelium (epiblastic in origin) of the foregut (Mansour) and the development of various glands (intestinal and gastric) from the epithelium of the gallbladder (King, 1930) support this suggestion. If this is so, then the raison d'être of Cohnheim's hypothesis disappears.

It is proposed to deal here with the observations made on four pathologic specimens, and to bring forward evidence from them that such tissue is not a "cell rest," does not arise during embryonic life and develops from differentiated tissue usually during postnatal, and most often in adult, life.

REPORT OF CASES

CASE 1.—S. D., a man, aged 37, complained of indigestion of two years' duration. Repeated roentgen examination revealed spasm of the wall of the stomach at the proximal end of the pyloric antrum, which was not completely relieved by the injection of atropine.

At laparotomy a localized nodular thickening, about three-fourths inch (1.87 cm.) in diameter, was found on the anterior surface of the stomach near the greater curvature, about 2½ inches (6.27 cm.) from the gastroduodenal junction. This was removed.

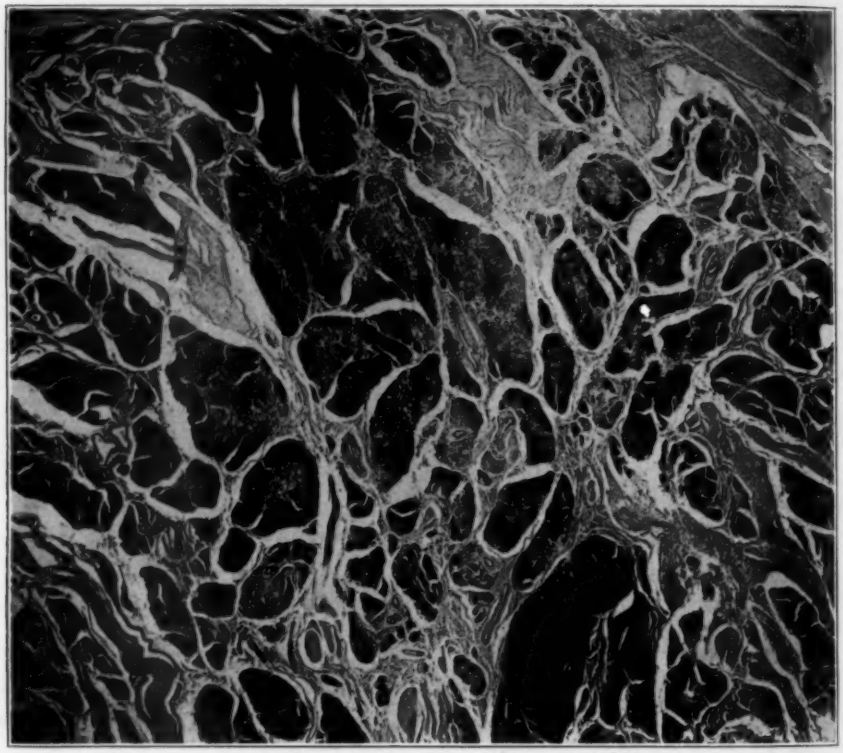

Fig. 1 (case 1).—Low power photomicrograph of a section of a nodule of pancreatic tissue in the wall of the stomach, showing the muscle bundles lying between the pancreatic lobules; × 24.

Microscopic examination showed that the tissue was composed almost entirely of pancreatic tissue lying between bands of muscle. Some of the tissue resembled pancreas, but was not completely differentiated (fig. 1).

CASE 2.—P. N., a man, aged 47, complained of indigestion of two years' duration. Vomiting had been becoming more severe for the four months before operation. Roentgen examination revealed an almost complete obstruction of the pylorus. Resection of the pyloric portion of the stomach (Polya's operation II) was performed.

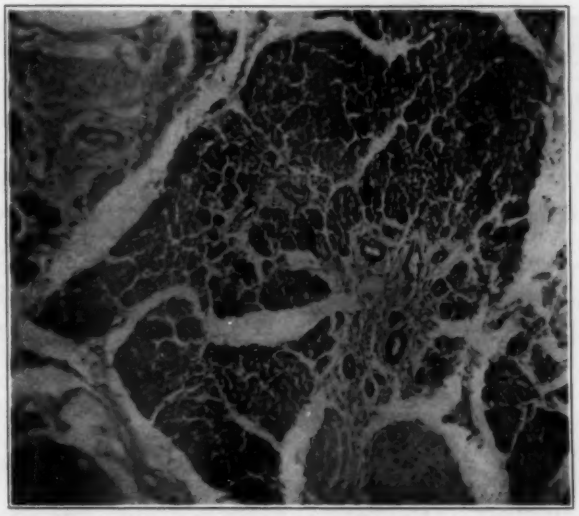

Fig. 2 (case 1).—Photomicrograph, showing the structure of the pancreatic tissue in a nodule in the wall of the stomach; × 100.

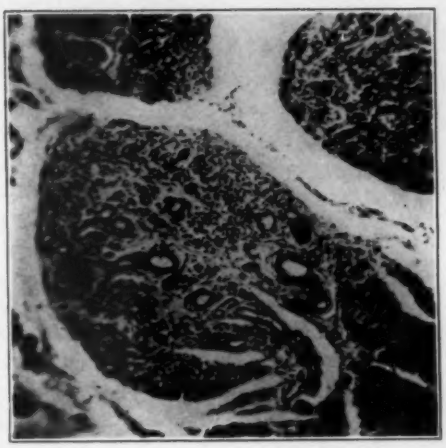

Fig. 3 (case 1).—Photomicrograph of a portion of tissue lying among the "pancreatic" lobules. This is not morphologically typical pancreatic tissue. There are many ducts and an indeterminate (? undifferentiated) type of epithelium; × 100.

Microscopically, the tissue consisted of masses of epithelial cells, mainly of the Brunner type, but some undifferentiated, and a few pancreatic acini. There was no evidence of malignant development.

CASE 3.—S. G., a man, aged 72, died of chronic nephritis and cardiovascular disease. Routine postmortem examination revealed a small thickening on the posterior surface of the stomach near the lesser curvature, two thirds the distance from the cardia to the pylorus. It measured one-fourth inch (0.64 cm.) in diameter.

Microscopically, well developed pancreatic tissue was found in the deep portion of the wall. Between this and the mucosa there was undifferentiated epithelium in the form of tubules lined by columnar epithelium. Some of the tubules were in close relationship with the mucosa, and others were closely connected and appeared to be continuous with the pancreatic tissue. In some places there were a few pancreatic alveoli in the submucous coat.

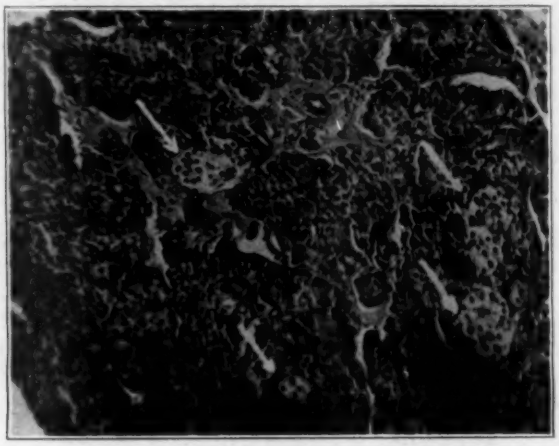

Fig. 4 (case 1).—Portion of pancreatic tissue in the wall of the stomach, showing islets of Langerhans (marked by arrows); × 140.

CASE 4.—A. V., a man, aged 53, reported at the hospital with symptoms suggestive of a chronic gastric ulcer. The diagnosis was confirmed by roentgen examination. Wide excision of an ulcer in the lower part of the cardia was performed.

Microscopic examination of the specimen showed remarkable epithelial proliferation in the neighborhood of the ulcer. Mucous glands, Brunner's glands and intestinal epithelium were present, and in a few areas there were groups of pancreatic acini (fig. 10).

COMMENT ON CASES

Three features of these cases are worthy of consideration.

1. *Age.*—All of the patients were relatively old, three being over 45. This fact was noted in many of the reports of examples of "cell rests." This observation alone should give one pause when attempting to explain the condition on a "congenital" basis. There is no reason why cellular

changes should not occur in children if the adequate stimulus were applied. Probably the absence of such phenomena in the young is to be correlated with their relative freedom from many chronic diseases. Hale reported a case of "pancreatic tissue" in the pylorus of an infant suffering from hypertonic stenosis of the pylorus. A brief scrutiny of his illustrations demonstrates that he apparently mistook Brunner's glands for pancreatic acini.

2. *History.*—The majority of patients give a history of symptoms of recent onset referable to the region involved. It is possible, of course, that the "rest" may have lain latent for fifty years and that another

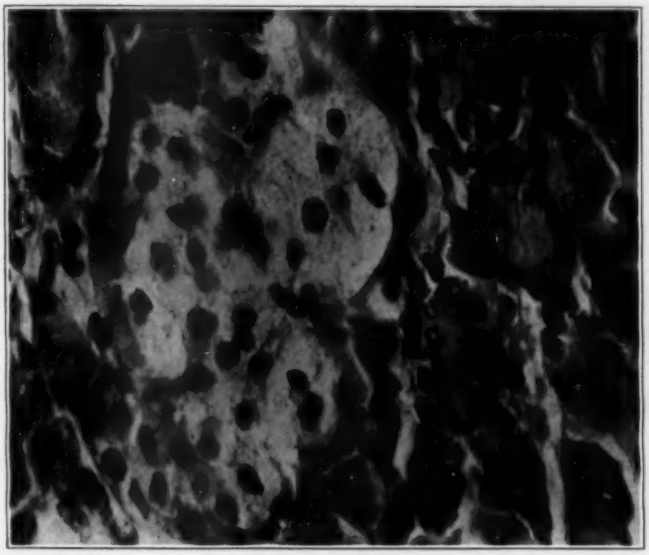

Fig. 5 (case 1).—High power view of an islet similar to those shown in figure 4; × 750.

lesion was superimposed on it, or even that it determined the site of the disease, e. g., ulcer. This is but multiplying hypotheses instead of proving them.

3. *Relationship to Inflammation.*—Evidence of inflammation is present in most cases, and since epithelial proliferation readily occurs in such areas, a close causative relationship of the epithelial structures to this process seems probable. Not only proliferation but metaplasia is frequently observed in association with an area of inflammation; e. g., various kinds of epithelium of the alimentary canal may be found in the chronically inflamed gallbladder (King); "gastric" glands have been found adjacent to a tuberculous ulcer of the colon (Nicholson, *b*), and

intestinal epithelium is a common finding in inflammatory conditions of the stomach.

In case 4 there was strong evidence of the recent development of pancreatic tissue directly from the gastric mucosa. Pancreatic tissue is associated with other epithelia; in the submucous layer it is closely associated with the gastric epithelium, and in some places it is directly continuous with it.

In case 3 there was no evidence of inflammation, but the pancreatic tissue was connected with the surface epithelium by ducts which were lined by cells that did not correspond with any normal adult type. The stimulus that caused its development had disappeared, or at least there was no evidence of its presence.

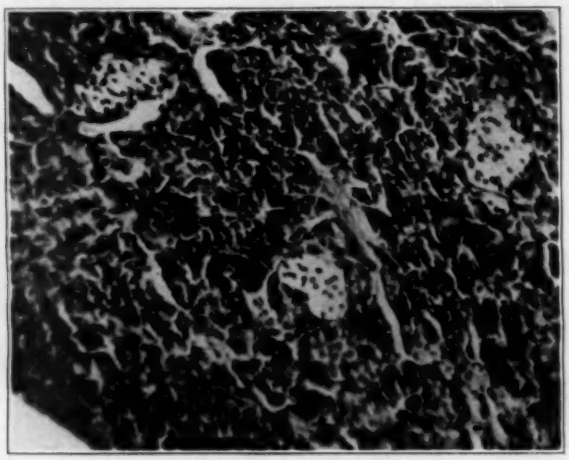

Fig. 6 (case 3).—Portion of pancreatic tissue showing islets; × 140.

MICROSCOPIC FINDINGS

The glands consist of collections of acini grouped in a characteristic manner. Among the acini there usually are groups of cells which morphologically correspond to islets of Langerhans.

The cells of the acini show two characteristic zones: an inner zone containing granules and an outer, nongranular zone, staining with hematoxylin and containing the nucleus. The cells appear to conform in all particulars with those of normal pancreas.

The tissue may appear in the subserous layer, in the muscular layer or in the submucous coat. From a consideration of the literature, Delhougne gave the distribution as in the accompanying table.

The frequency of occurrence of aberrant pancreatic tissue corresponds closely to the distribution of peptic ulcer of the stomach. Most

observers agree that ulceration of the stomach is a postnatal development and due to definite pathologic phenomena. This similarity of distribution forms another link in the chain of evidence for a postnatal origin of the pancreatic tissue, more especially since the distribution is not readily explicable embryologically.

In all of these situations the glandular tissue is intimately mingled with the tissue of the part; e. g., when glandular tissue is present in the muscular coat, the groups of acini lie among the muscle bundles. This, in itself, seems to put considerable difficulty in the way of accepting the hypothesis of a "rest." If a "rest" of pancreatic tissue occurred in the wall of the stomach, one would expect that in its growth it would displace contiguous material, and that it would resemble the normal gland, which does not contain bands of muscle between the groups of acini.

Delhougne's Distribution of Tissues

Cases	Location	Percentage	
15	Submucous	45.4	33 cases
5	Intramural	15.1	
5	Subserous	15.1	
8	More than one layer	24.2	
14	Pylorus	58.3	24 cases
3	Greater curvature	12.5	
5	Lesser curvature	20.8	
2	Cardia	8.3	

The close association of the pancreatic tissue with muscle bundles is similar to the association of glands which have grown down from the epithelium in cases in which the epithelium is stimulated, e. g., in the neighborhood of a gastric ulcer.

Islets of Langerhans are frequently found throughout the tissue. Characteristically, they are present in the masses of pancreatic alveoli, but in other parts they may be found alone or in association with ducts (fig. 8). In some cases they have been found arising apparently from acini, either as an outgrowth from the acinar tissue (fig. 9), or by a change in the acini themselves (fig. 5).

Atypical cells and acini form groups among the typical pancreatic tissue. Some of them form complete groups not connected with the contiguous pancreas, but in other cases they merge into the pancreatic acini so that a portion of a mass of acini is pancreas and the remainder is atypical in character.

These associated acini are less deeply staining than those of the true pancreatic type; they are slightly larger, and many of them have a small central space. The cells are of about the same size as the pancreatic cells; the protoplasm has few or no deeply staining granules, and the nuclei are more vesicular and have less deeply staining chromatin.

Ducts lined by cuboidal epithelium and with a well formed muscular coat are found among all the cell groups, whether typical or atypical in appearance. In many cases the ducts may be found in deeply situated masses, passing up through the wall of the stomach to the mucous surface. Here again a serious difficulty is opposed to the acceptance

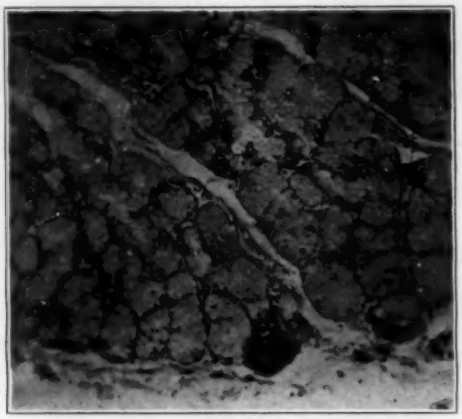

Fig. 7 (case 2).—Photomicrograph of a portion of the wall of the stomach, showing Brunner's glands and one acinus of the pancreatic type. There were other typical pancreatic lobules in the vicinity; × 165.

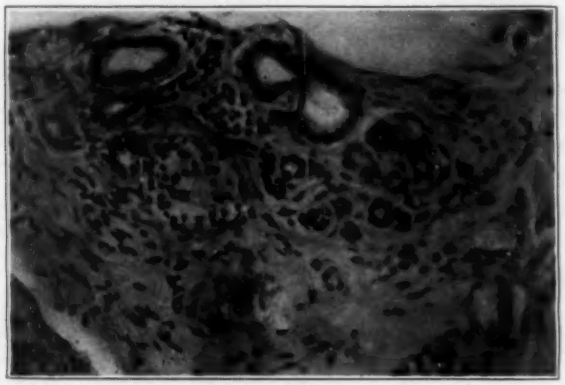

Fig. 8 (case 3).—Photomicrograph of portion of a section of the nodule. There are well formed islets among the ducts; × 140.

of some phases of the hypothesis of a "rest." Misplaced tissue should, by the course of its ducts, show some indication of its origin, and the ducts should run along the wall toward the duodenum. In fact, they are continuous with the mucosa that lies above, irrespective of whether it is stomach, intestine or Meckel's diverticulum. The biologic meaning

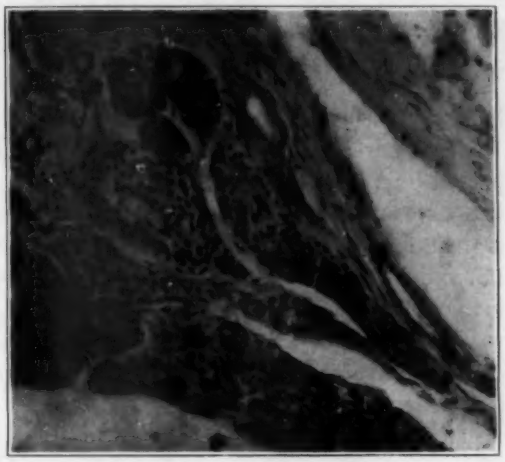

Fig. 9 (case 3).—Another portion of the nodule, showing a continuity between alveoli and islet tissue; × 140.

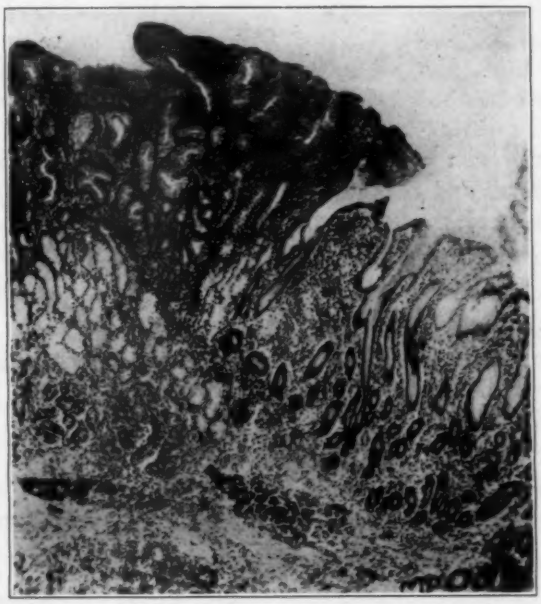

Fig. 10 (case 4).—Photomicrograph of a portion of the mucosa of the stomach, showing epithelial proliferation and metaplasia, with the formation of pancreatic lobules; × 38.

of this peculiarity according to the hypothesis of a "rest" is at least nebulous.

The pancreatic tissue may be independent of other epithelial structures (case 1, fig. 1); it may be associated with atypical (probably undifferentiated) tissue (case 3), or it may be associated with other glandular elements (case 4, fig. 10). This pancreatic tissue is sometimes related to the other glands by way of undifferentiated tissue, as in the case reported by Woolsay and Millzner.

Our observations confirm this relationship. It is one which strongly suggests that a glandular tissue (e. g., Brunner's glands) has undergone dedifferentiation, and that the cells have been differentiated to form the pancreatic tissue. In some parts of the body, e. g., in the gallbladder, it is possible to find glands of an unusual form ("aberrant") in close association with the normal cells of the part and almost certainly arising from them without any intermediate stage. Presumably in such cases the intermediate step has passed, and one has to postulate such a stage from the morphologic appearances.

In the stomach a similar appearance may be encountered. At the edge of a mass of Brunner's glands a single acinus resembling a pancreatic gland may be found (fig. 7). Apart from its morphology, its nature is suggested by the presence of pancreatic tissue in the neighborhood.

SUMMARY

1. From a study of four cases of pancreatic tissue in the wall of the stomach and a review of the literature it is concluded that pancreatic tissue arises from the epithelium of the stomach under the action of abnormal stimuli and does not arise as a "cell rest" from the displacement of a pancreatic anlage during embryonic life.

2. The reasons for this conclusion are:

(*A*) Such tissue is connected directly or indirectly with the overlying epithelium.

(*B*) Continuity of such tissue with the gastric epithelium can undoubtedly be directly traced in some cases.

(*C*) The tissue is found mainly (if not entirely) in adults and mainly in old people, thus suggesting a postnatal development.

(*D*) The distribution of pancreatic tissue in the stomach corresponds to that of obviously acquired lesions, such as a gastric ulcer.

(*E*) No morphologic connection is found between these masses and the anatomic pancreas.

(*F*) The pancreatic tissue does not occur as a discrete mass of tissue occupying a portion of the wall, but is intimately mingled with the structures of the wall of the stomach.

3. Reasons are given for considering that the various embryologic "explanations" which have been proposed are inadequate and do not take cognizance of known embryologic laws.

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EXPERIMENTAL OCCLUSION OF THE PULMONARY ARTERY

AN ANATOMIC STUDY

CYRUS F. HORINE, M.D.
AND
C. GARDNER WARNER, M.D.
BALTIMORE

The increasingly frequent occurrence of postoperative pulmonary embolism with its dreaded and often fatal results is probably responsible for the stimulation of interest in the subject of experimental occlusion of the pulmonary artery. Numerous investigators have approached the subject from as many different angles. The literature has been reviewed by Schlaepfer.[1] Experiments performed by this investigator on rabbits and dogs showed that ligations of a branch of the pulmonary artery did not result in marked fibrosis as had been shown by Bruns,[2] Sauerbruch,[3] Kawamura,[4] Smirnoff[5] and others. Schlaepfer did produce extensive fibrosis, however, by cutting the phrenic nerve when ligating the corresponding pulmonary artery. Schlaepfer's experiments on dogs were carried out, however, through a transpleural approach. In the experiments on rabbits the branch of the pulmonary artery was ligated through a pericardotomy opening without causing pneumothorax.

In any mechanism so complicated as that of the so-called cardiorespiratory apparatus, in which there is so much interdependence, the changes in pressure caused by operative pneumothorax might materially alter the subsequent anatomic findings.

This article will deal chiefly with the anatomic findings in the dog's lung subsequent to ligation of the right pulmonary artery or one of its branches. A method of exposure of the pulmonary vessels devised by

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From the Departments of Surgery and Pathology of the University of Maryland School of Medicine.

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one of us (C. F. H.[6]) was used in these experiments. This method interferes less with the normal physiologic activity of the cardiorespiratory mechanism, both during the experiments and after recovery, than either the transpleural or the transpericardial approach.

EXPERIMENTAL METHOD

Young normal dogs, preferably of the terrier, beagle or bull types, were used in these experiments. The broad chest and rather short neck which characterize dogs of these types favored exposure of the mediastinal vessels. The dog was anesthetized with ether, and under aseptic technic an opening was made in the mediastinum through a longitudinal incision over the trachea. From this incision the dissection was carried down through the thorax between the pleural cavities on either side, to the base of the heart. A small incision was made in the connective tissue which covers the pulmonary artery outside of the pericardium. A ligature was passed around the right branch or its secondary division with an aneurysm needle. This ligature was tied by using long clamps. Two ligatures may be applied, between which the artery may be severed. The animals were killed after variable periods ranging from one week to fifteen months, although the anatomic changes as recorded in the x-ray pictures were followed in several animals beginning a few hours after ligation of the pulmonary artery. In each instance the animals were killed by deep ether anesthesia. The trachea was clamped before the animal ceased to breathe. An injection of a diluted solution of formaldehyde, U. S. P. (1:10), into the trachea was made to fix the lungs before collapse. After a small amount of formaldehyde was introduced, another needle was placed in the trachea to allow air to escape. The formaldehyde was injected slowly by gravitation, and the injection was completed when the solution began to flow from the second needle. The chest was opened after from fifteen to twenty minutes. The common carotids, thoracic aorta and venae cavae, as well as the trachea, were ligated before the thoracic contents were removed. The heart and lungs were then placed in formaldehyde for twenty-four hours.

EXPERIMENTAL RESULTS

In none of the dogs was there any deformity of the chest, but when the thorax was opened in 2 dogs in which the entire right pulmonary artery had been ligated, the heart and mediastinum were found displaced toward the side of the ligation. In all the dogs the operative wound in the mediastinum healed without infection, and at autopsy only a few adhesions in the mediastinum around the pulmonary vessels were encountered. In several of the dogs metal skin clips were used to occlude the branches of the pulmonary artery; in others, either single or double silk ligatures were used. In the two dogs in which the pulmonary branch had been ligated for fifteen months, the lumen of the occluded branch was obliterated and only a fiber-like cord remained. In those in which the ligation was of shorter duration, the lumen of the ligated vessel contained organized thrombi. The lung or lobe supplied by the

6. Horine, C. F.: Mediastinotomy for Experiments on the Heart and Lungs in the Dog, J. Thoracic Surg. **2**:77, 1932.

ligated vessel was always smaller than the intact one. The pleural sacs of the dogs showed no adhesions or excess fluid, although the visceral pleura in some showed definite thickening. There was always a tendency toward "wrinkling" of the visceral pleura over the lobes in

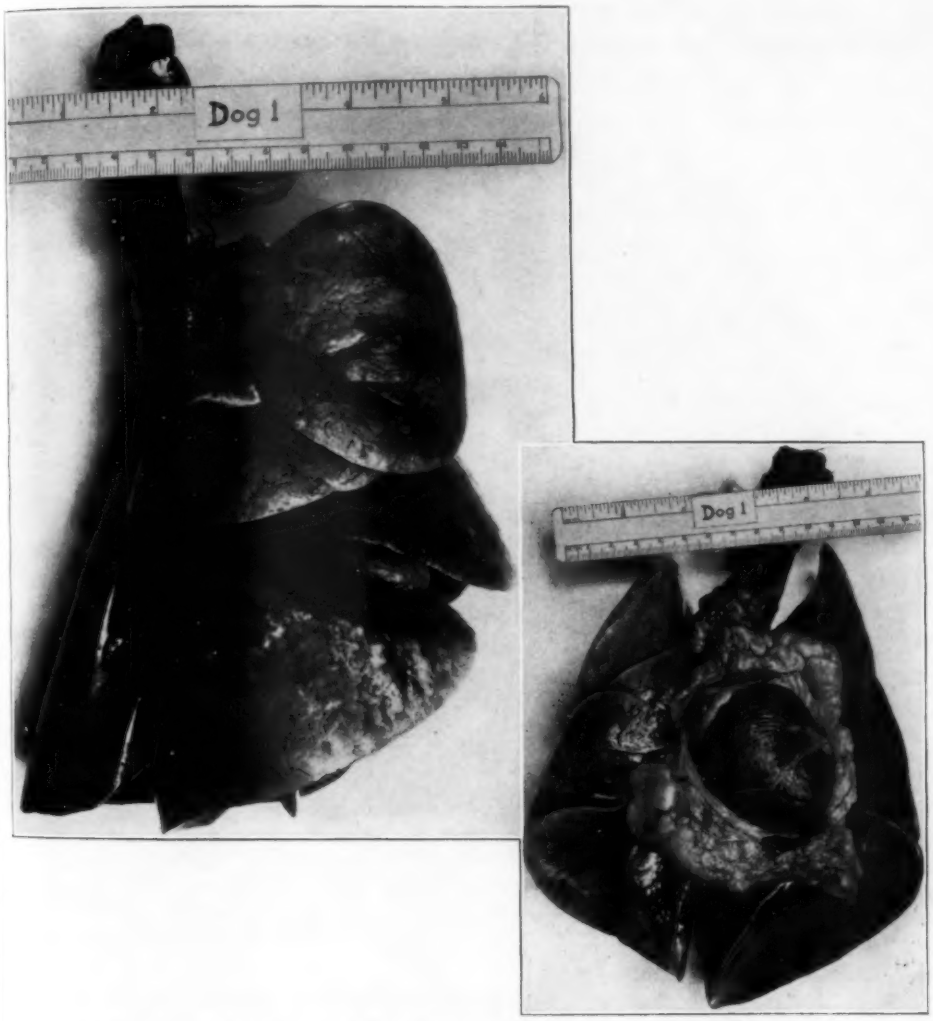

Fig. 1 (dog 1).—Lateral view of the upper lobe of the right lung, taken fifteen months after ligation of the pulmonary artery which supplied the lobe. Note the presence of small pleural vessels in the upper lobe. The lower lobe, supplied by the unligated artery, does not have macroscopic vessels. The inset shows the anterior view of the heart and lungs of the same dog.

which the branch of the pulmonary artery had been occluded. Areas of emphysema could be demonstrated in both lungs, especially in the lobe supplied by the nonligated branch. Several of the lungs supplied by ligated branches showed gross evidence of old hemorrhage into air sacs, with some organization. These areas were unlike infarcts in that there was no dulling of the pleura or collection of fibrin on its surface. Practically all of the dogs had enlargement of the right ventricle, and

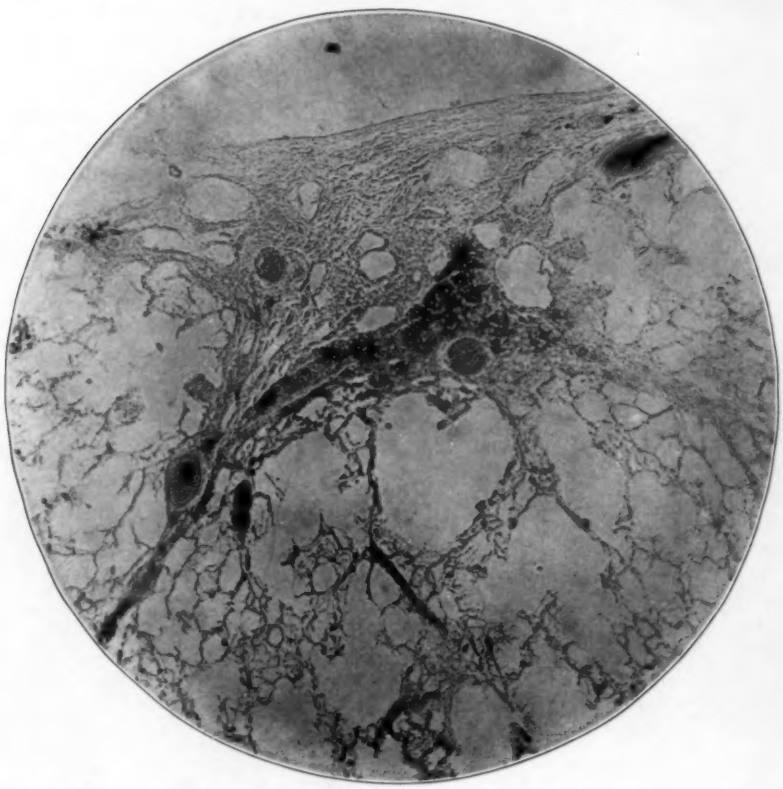

Fig. 2 (dog 1).—Photomicrograph of an unstained frozen section taken from the upper lobe of the right lung. Note the increase in perivascular connective tissue; × 80.

in some cases a deep sulcus could be seen between the apexes of the ventricles. There was little evidence of an increase in the thickness of the visceral pleura except in the dogs in which a branch of the pulmonary artery had been ligated fifteen months previously. The increase in connective tissue in these two cases was for the most part subpleural, although there was some increase in the amount of fibrous tissue in the interstitial spaces under the pleura, as shown in figures 1 and 2. Particular attention is called to the prominence of subpleural vessels over

the lobes supplied by the ligated artery. These are either new vessels or preexisting bronchial vessels the caliber of which has increased since ligation.[7] Some of these vessels measured as much as 1 mm. in diameter. The fact that such prominent subpleural vessels were not found on the side of the unligated artery seems to indicate that these vessels are concerned in the compensatory mechanism following pulmonary occlusion. They may possibly represent a collateral anastomosis between bronchial and pulmonary vascular systems. That many of these subpleural vessels

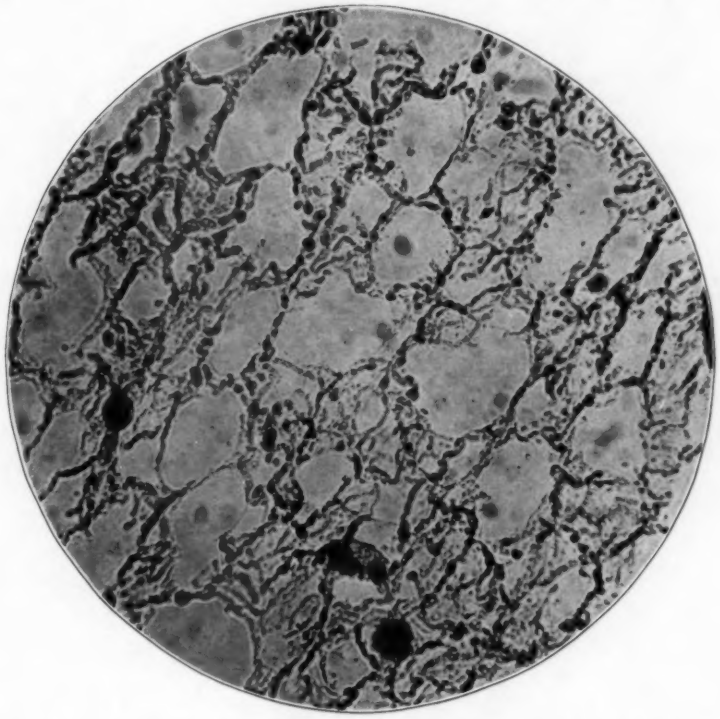

Fig. 3 (dog 1).—Photomicrograph of a thick, frozen section of the upper lobe of the right lung fifteen months after ligation of the pulmonary artery that supplied the lobe. Note the uniformity in size of the alveoli and of the interalveolar capillaries; × 135.

are derived from the bronchial vascular system was shown by us by the injection of pigment.[7] One would think that adhesions would develop between the visceral and the parietal pleura as a means of establishing a collateral circulation with vessels of the wall of the chest, but this was not the case in any of the eight experiments. Definite

7. Horine, C. F., and Warner, C. G.: Distribution of the Pulmonary Circulation in the Dog, J. Thoracic Surg. **2**:80, 1932.

enlargement of the bronchial arteries and of their branches anastomosing with the esophageal artery could be seen without the injection of pigment four weeks after ligation of the right pulmonary artery.

Microscopic examination of the intact lung showed interesting changes. Some of the changes could be seen as early as two hours after ligation of a branch of the pulmonary artery. These findings, after ligations of such short duration, were observed by us in connection with experiments on the pathologic physiology following occlusion. The

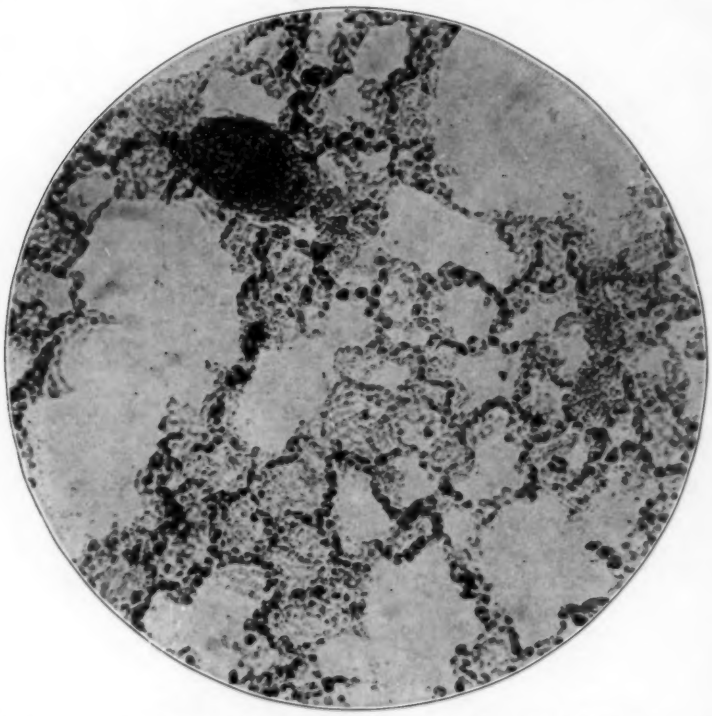

Fig. 4 (dog 1).—Photomicrograph of an unstained, thick, frozen section of the upper lobe of the left lung. The pulmonary artery supplying this lobe was not ligated. Note the areas of emphysema and the increase in interalveolar capillaries; × 135.

pathologic changes consisted chiefly of enlargement of the alveolar sacs with rupture and fragmentation of the walls. The interalveolar capillaries were enlarged and dilated. These changes were most marked about four weeks after ligation; in fact, there seemed to be a basket-like network of capillaries in each alveolar wall, as shown in figure 5. The increase in size of the individual alveolus, together with the compensatory emphysematous condition of the whole lobe or lobes of the lung on the side of the nonligated artery, would account for the increase

in size and probably contribute toward the displacement of the heart and mediastinum toward the side of the ligated artery. An immediate decrease in the volume of the lung, or at least a decrease in the volume of the blood, is expected after occlusion of its corresponding artery. With the decrease in the volume of the blood there should be an increase in the negative intrapleural pressure, because as the total volume of the lung on the side of the ligated artery is decreased the size of the potential space on that side should be increased. If a simultaneous compensatory

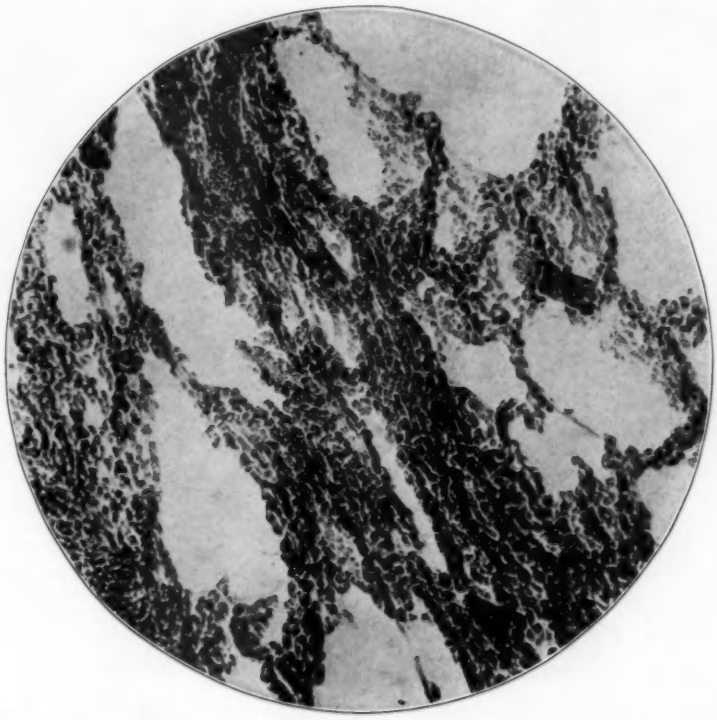

Fig. 5 (dog 4).—Photomicrograph of the lobe of the right lung between three and four weeks after ligation of the corresponding pulmonary artery. Note the area of compression of the alveoli and the surrounding areas of emphysema. Stained with hematoxylin and eosin; × 135.

increase in total volume occurs in the lung on the side of the nonligated artery, a displacement of the structure lying between the two lungs to the affected side should be expected. Figure 7 shows a marked displacement of the apex of the heart to the right. This occurred within ninety-six hours after ligation of the right pulmonary artery. These changes in the volume and pressure could also account for the emphysema.

A microscopic picture of a lung in which a branch of the pulmonary artery had been ligated showed anatomic changes which are difficult to explain. The findings early after ligation consisted of areas of emphysema, as well as of collapse or atelectasis, areas which appeared to show compression of a number of alveoli and their corresponding interalveolar capillaries. Surrounding these areas of compression were found emphysematous sacs with hemorrhage into many alveoli. In some sections, especially those near the periphery of the lung, solid

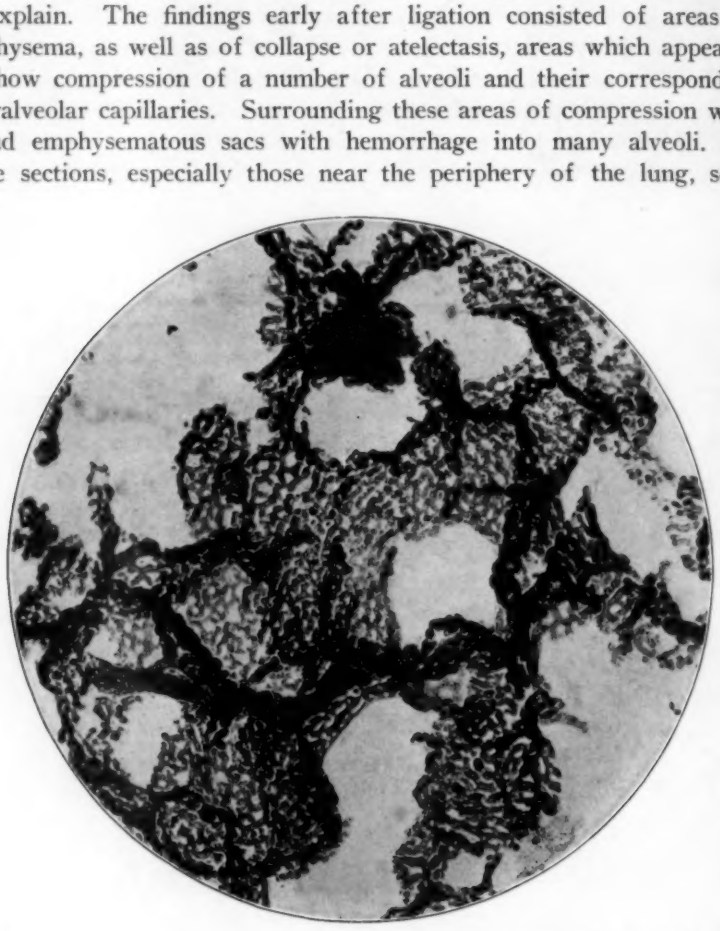

Fig. 6 (dog 4).—Photomicrograph of a thick, frozen section of the lobe of the left lung the pulmonary artery to which was not ligated, taken between three and four weeks after ligation of the right pulmonary artery. Note the areas of emphysema and the more numerous interalveolar capillaries. Stained with hematoxylin and eosin; × 135.

masses of hemorrhage were noted beneath an intact pleura, without exudation on, or thickening of, that membrane. In not a single instance were adhesions found between the opposing pleural surfaces where this type of hemorrhage existed, even in specimens which showed some evidence of organization of the hemorrhage. Deeper in the pulmonary tissue, that is more centrally, the hemorrhage was less evident.

Only in the two dogs in which a branch of the pulmonary artery had been ligated fifteen months previously was there an increase in the interstitial connective tissue, and in these it was very slight and confined chiefly to subpleural thickening. It was most evident around the visceral pleural vessels previously mentioned. In these two dogs, the general histologic appearance of the pulmonary tissue in the lobes on the side on which the pulmonary artery had been ligated was that of air sacs of uniform size, but somewhat smaller than normal. There was also

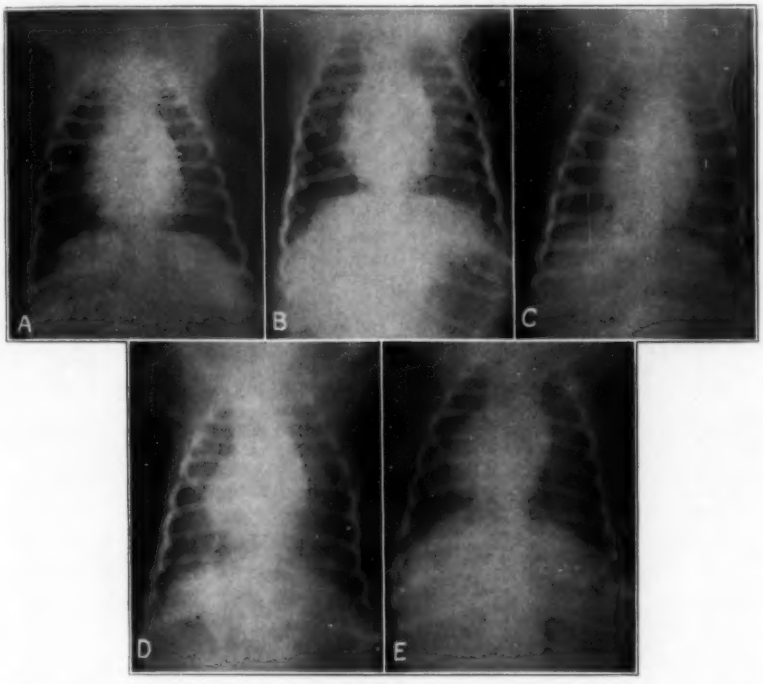

Fig. 7 (dog 7).—Series of roentgenograms showing the displacement of the heart that follows ligation of the pulmonary artery. The right pulmonary artery had been ligated. No attempt was made to bring out the details of the lung. Several of the plates suggest the presence of pneumothorax. The shadows which suggest pulmonary tissue have been cast by the redundant mammary glands of the female dog used in this experiment. It is difficult to obtain accurate plates when the dog is used, but there is very little rotation, if any, in these plates. Note the gradual displacement of the heart and mediastinum toward the right side, or the side of the ligated artery. *A* was taken immediately before ligation; *B*, half an hour afterward; *C*, twenty-four hours afterward; *D*, seventy-two hours afterward; and *E*, ninety-six hours after ligation.

uniformity in the size and the number of capillaries. The basket-like capillary plexus in the alveoli which is present in the normal dog's lung to a modified degree was entirely absent in these two dogs.

Observations on Dogs Studied

Dog	Date and Operation	Course and Symptoms	Roentgenograms Taken	Date of Autopsy	Duration of Experiment	Gross Anatomic Changes	Microscopic Anatomic Changes
1. Black and white terrier	March 18, 1930, mediastinotomy; ligation of right superior pulmonary artery	Wound healed per primam in 10 days; entire course without respiratory or cardiac symptoms; dog gained weight	March 25, April 1 and 8 and July 3, 1930; Feb. 6, 1931	June 10, 1931	15 months	Ligature intact; pulmonary vessel to upper lobe cordlike; heart hypertrophied and dilated, especially on the right side, with a sulcus between the ventricles at the apex; no adhesions over "ligated lobe"; no free fluid; "ligated lobe" small and shrunken, with the visceral pleura showing a tendency toward wrinkling	Increased subpleural connective tissue, especially in interstitial spaces around vessels; hypertrophy of preexisting bronchial vessels in pleura; compensatory emphysema of intact lung; increased number of interalveolar capillaries; scattered areas of emphysema and atelectasis of "ligated" lobe; obliteration of groups of sacs from organization of hemorrhage; decreased number of interalveolar capillaries in "ligated" lobe
2. Mixed fox terrier and beagle	April 10, 1930, mediastinotomy; ligation of right inferior pulmonary artery	Wound healed in 7 days; recovery without symptoms	April 17 and 25, 1930, and Feb. 6, 1931	July 10, 1931	15 months	Ligature intact; pulmonary vessel to lower lobe obliterated; heart hypertrophied; no free fluid in pericardium; right lower lobe somewhat shrunken, with gross areas of hemorrhage under the pleura; no inflammatory reaction on the overlying pleura; some compensatory emphysema of the opposite lung	The same general findings as in dog 1
3. Mixed bull and beagle	May 19, 1931, mediastinotomy; ligation of right pulmonary artery	Recovery complete and wound healed in 7 days; no cardiorespiratory symptoms	.....	June 2, 1931	2 weeks	Ligature intact; right pulmonary artery showed a thrombus in lumen; right side of heart dilated; right lung smaller; compensatory emphysema on left	No increase in connective tissue in interstitial tissue; scattered areas of emphysema and atelectasis, with hemorrhage into air sacs at periphery of lung without pleural reaction
4. Tan mongrel	May 18, 1931, mediastinotomy; ligation of right pulmonary artery	Recovery complete; no symptoms throughout experimental period	.....	June 8, 1931	3 weeks	Ligature intact; right pulmonary artery grossly occluded; ligated lung small	No increase in connective tissue in interstitial tissue; scattered areas of emphysema, atelectasis and hemorrhage of "ligated" lung; compensatory emphysema of intact lung
5. Black mongrel	Jan. 11, 1931, mediastinotomy; ligation of right pulmonary artery	Recovery uneventful and without cardiac or respiratory symptoms	5 cc. of iodized oil 10 minutes after ligation; Jan. 12 and 13, 1931	Jan. 18, 1932	1 week	Ligature intact; right pulmonary artery occluded; patchy atelectasis	No increase in connective tissue in subpleural or interstitial tissue; many areas of collapse
6. Beagle	Jan. 18, 1932, ligation of right pulmonary artery	Shortness of breath throughout course	Jan. 25, 1932; enlarged heart	Feb. 1, 1932	2 weeks	Ligature on right pulmonary artery intact; heart enlarged and dilated, with sulcus between ventricles; no adhesions; no free fluid in cavities of chest	No increase in interstitial connective tissue; scattered areas of emphysema, atelectasis and hemorrhage in "ligated" lung
7. Black and white mongrel	Jan. 19, 1932, mediastinotomy; ligation of right pulmonary artery	Recovery without symptoms; found dead 2 weeks after operation	½ hour, 24 hours, 72 hours and 96 hours after ligation	Found dead Feb. 2, 1932	2 weeks	Ligature intact; no inflammation in mediastinum; heart enlarged and displaced to right; right lung small; no gross explanation as to cause of death found	No increase in interstitial connective tissue; areas of atelectasis numerous; with hemorrhage in air sac in "ligated" lung; "intact" lung emphysematous
8. White and tan mongrel	Jan. 27, 1932, mediastinotomy; ligation of right pulmonary artery	Recovery uneventful	Jan. 28 and 29, 1932	Feb. 14, 1932	18 days	Ligature intact; "ligated lung" small, with tendency toward "wrinkling" of visceral pleura; heart enlarged and displaced toward affected side	Pulmonary artery occluded by an organizing thrombus; no increase in subpleural or interstitial connective tissue; scattered areas of emphysema and atelectasis, together with hemorrhage in air sac noted in "ligated" lung

CONCLUSIONS

1. Scattered areas of emphysema, atelectasis and hemorrhage into the air sacs are produced in the lung by ligating a branch of the pulmonary artery.

2. If the ligation of a branch of the pulmonary artery is performed extrapleurally without pneumothorax, it does not produce a deformity of the chest with marked fibrosis and contraction in fifteen months.

3. Ligation of a branch of the pulmonary artery results in new formation of vessels in the visceral pleura or in an increase in the caliber of preexisting ones.

4. Displacement of the heart and mediastinum to the side of the ligated artery may be seen with the x-rays as early as forty-eight hours after occlusion of the artery.

EXPERIMENTAL OCCLUSION OF THE PULMONARY ARTERY

PATHOLOGIC PHYSIOLOGY

CYRUS F. HORINE, M.D.
AND
C. GARDNER WARNER, M.D.
BALTIMORE

Welch,[1] Plumier,[2] Tigerstedt,[3] Underhill[4] and others have stated that ligation of the pulmonary artery of one lung causes very little or no change in the systemic blood pressure. Haggart and Walker[5] found no significant variation in the general circulation of animals until from 52 to 66 per cent of the pulmonary circulation had been occluded. Tigerstedt[3] showed that there was a slight decrease in the volume output of the left ventricle per minute after one branch of the pulmonary artery had been ligated. Lichtheim[6] found no significant variation of the general circulation after occluding 75 per cent of the pulmonary circulation. Mann,[7] producing pulmonary embolism by the introduction of clots into the venous system (the femoral vein), noted a slight drop in the systemic pressure, which he believed to be due to the passage of the embolus through the valves of the heart. Underhill[4] stated that ligation of the left pulmonary artery in cats (with the chest open and under positive pressure anesthesia) caused an increase in pulmonary arterial pressure from 25 to 60 per cent. He found no effect on the carotid blood pressure, the pulse rate, the output of the heart or its state of dilatation. Haggart and Walker[5] measured the blood pressure in the femoral artery after occluding the pulmonary artery. They clamped the left pulmonary artery and the main pulmonary artery with a special

From the Departments of Surgery and Pathology of the University of Maryland School of Medicine.

1. Welch, W. H.: Zur Pathologie des Lungenödems, Virchows Arch. f. path. Anat. **72**:375, 1878.

2. Plumier, L.: La circulation pulmonaire, Arch. internat. de physiol. **1**:176, 1904.

3. Tigerstedt, R.: Ueber den Lungenkreislauf, Skandinav. Arch. f. Physiol. **14**:259, 1903.

4. Underhill, S. W. F.: An Investigation into the Circulation Through the Lung, Brit. M. J. **2**:779, 1921.

5. Haggart, G. E., and Walker, A. M.: The Physiology of Pulmonary Embolism as Disclosed by Quantitative Occlusion of the Pulmonary Artery, Arch. Surg. **6**:764 (May) 1923.

6. Lichtheim, L.: Die Störungen des Lungenkreislaufes und ihr Einfluss auf den Blutdruck, Inaug. Dissert., Breslau, 1876.

7. Mann, F. C.: Pulmonary Embolism: An Experimental Study, J. Exper. Med. **26**:387, 1917.

graduated clamp which was applied through an opening in the wall of the chest. They concluded that with this method it was possible, in the normally breathing dog, to produce partial or complete block of the pulmonary artery, the condition as here brought about being analogous to pulmonary embolism in man. Clamping of the left branch of the pulmonary artery caused an immediate rise in the pulmonary pressure, the increase averaging about 30 per cent. This procedure caused no significant change in the general systemic pressure, or any variation in the size, rate or output of the heart. Ventilation as measured by a spirometer was, however, increased approximately 25 per cent, a moderate hyperpnea resulting. Following total occlusion of the pulmonary artery an immediate reaction occurred; the heart dilated quickly to a marked degree, and the volume output per minute became materially less. The pulmonary pressure rose sharply from 121 to 267 per cent, and then gradually fell to zero. The systemic pressure began to fall immediately and did not recover, while respirations became irregular and shortly thereafter ceased altogether.

Complete obstruction of the main pulmonary artery causes immediate death, and fatalities also occur following unilateral pulmonary embolism, although therapeutic ligation of a main branch of the pulmonary artery in the human being has been followed by recovery (Sauerbruch,[8] Meyer[9] and others). Ligation of a main branch of the pulmonary artery in the dog is fatal only in exceptional cases. The present study was undertaken with the hope that some light might be thrown on the question of the compensatory mechanism following partial pulmonary occlusion.

EXPERIMENTAL METHODS

Twenty-three dogs were used in these experiments. In all instances, the studies were carried out without pneumothorax by a method of mediastinotomy devised by one of us (C. F. H.).[10] An incision was made over the trachea and the dissection continued through the mediastinum to the pulmonary artery between the two pleural spaces.

The artery was occluded either with a clamp or with an untied ligature. The latter method was preferred, since it was less damaging to the wall of the vessel. By the use of an aneurysm needle a ligature was passed around the artery, and occlusion was produced by traction.

RESULTS

Contrary to the opinion of others, it was found that the occlusion of one half of the pulmonary artery, i. e., one main branch, will cause a decrease in the systemic pressure of from 10 to 30 mm. of mercury.

8. Sauerbruch, F.: Die Bronchiektasien, 3me Congrès Soc. internat. de chir., Bruxelles, 1911.

9. Meyer, W.: Surgery of the Pulmonary Artery, Ann. Surg. **32**:189, 1913.

10. Horine, C. F.: Mediastinotomy for Experiments on the Heart and Lungs in the Dog, J. Thoracic Surg. **2**:77, 1932.

This drop usually occurs within four seconds and is followed by a compensatory rise which is carried above the normal pressure line. The compensatory rise in pressure requires from ten to thirty seconds; it varies in the individual animal. Following the rise there is a recession to the normal base line. Thus, an S-shaped curve is produced. This curve is typical of the changes in pressure in the systemic circuit following occlusion of a branch of the pulmonary artery. If the occlusion is released when the carotid pressure returns to the normal base line, another positive curve appears; this is of short duration.

The original decrease in carotid pressure is no doubt due to a decrease in the output of the left ventricle, since, for a time at least, the amount of blood returned to the heart through the pulmonary veins must be reduced. The following questions then arise: What produces the compensatory rise to and above the normal base line, and if the mechanism by which this is produced should be absent or impaired, would the animal not succumb? Is the duration of the systole increased to help maintain a normal pressure? Do the interalveolar capillaries of the unligated lung dilate sufficiently to allow an increase in volume to the left side of the heart? Is there a reflex stimulation of the vasoconstrictors in order to increase peripheral resistance and thereby maintain normal systemic pressure?

The compensatory rise in pressure may be due to one or several combined mechanisms. The same type of curve is obtained if the pulmonary artery is occluded after both vagi have been severed or the animal has been atropinized. In several animals the vagi were cut and the spinal cord severed at the seventh cervical segment. According to Keng,[11] the phrenic nerve in the dog arises from the fifth and sixth cervical segments.

An immediate decrease in pressure occurs after section of the cord. After the pressure has established a normal base line the right pulmonary artery is occluded. An immediate decrease in the systemic pressure develops without the usual compensatory rise. If the artery remains obstructed, the dog will die. A dog the vagus and cord of which were sectioned was given epinephrine to obtain an epinephrine curve, and after the circulation had been reestablished following the injection of epinephrine another dose was given. At the beginning of the epinephrine curve, the right pulmonary artery was occluded. There followed an immediate decrease in the carotid pressure, with a subsequent compensatory rise. The occlusion of the pulmonary artery was then released, and a greater rise occurred. On the fall of the epinephrine curve, the right pulmonary artery was occluded again. An abrupt fall in systemic pressure was noted, but the usual compensatory rise in

11. Keng, L. B.: On the Nervous Supply of the Dog's Heart, J. Physiol. **14**: 467, 1893.

pressure did not follow. The pressure continued to decrease until the occlusion had been released. In the dog, the vagus and cord of which are sectioned, plus occlusion of the right pulmonary artery at the time of the rise in the epinephrine curve, the compensatory rise after occlusion will be in proportion to the amount of epinephrine given.

ILLUSTRATIONS

The illustrations are photographs of kymographic tracings made in experiments 2, 10, 5, 13, 7 and 4. The top line in each illustration is the respiratory record, the middle line is the carotid blood pressure curve (except in experiment 13, the pressure was recorded from the femoral artery), and the lower line represents time.

Fig. 1 (experiment 10).—The typical S-shaped curve of the carotid blood pressure record produced by occlusion of the right pulmonary artery. *CP* marks the point of occlusion of the pulmonary artery. The occlusion was released at *RP*. The markings are timed to two seconds. In addition to the S-shaped curve, note the momentary decrease in amplitude of respirations at *CP* and the increase in pressure at *RP*. The blood pressure was measured in millimeters. A decrease of 26 mm. occurred at *CP*.

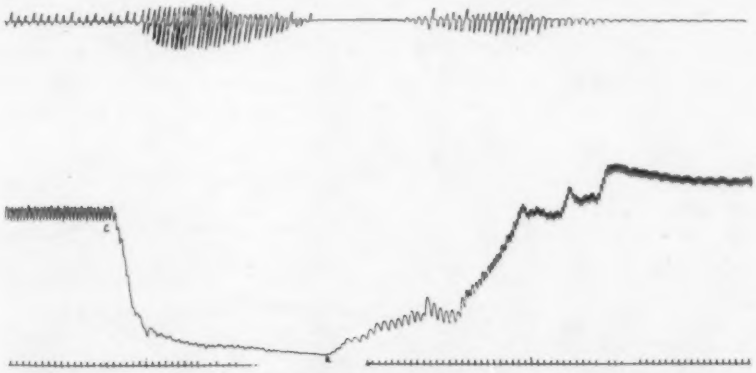

Fig. 2 (experiment 2).—Between 75 and 100 per cent of the pulmonary artery was occluded at *C* and released at *R*. A decrease of 77 mm. occurred in seven seconds. Note the increase in rate and amplitude of respiration during the decrease in blood pressure.

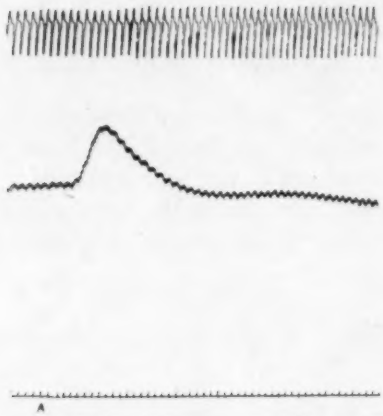

Fig. 3 (experiment 5).—Epinephrine curve. One minim (0.06 cc.) of epinephrine was injected intravenously at *A*. Time in seconds.

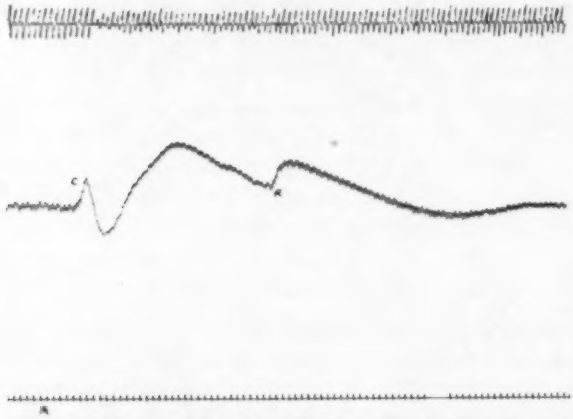

Fig. 4 (experiment 5).—One minim (0.06 cc.) of epinephrine was injected at *A*. On the rise of pressure, the right pulmonary artery was occluded at *C* and released at *R*. Note the exaggerated S-shaped curve with a quicker return to the normal base line after occlusion at *C*. Time in seconds.

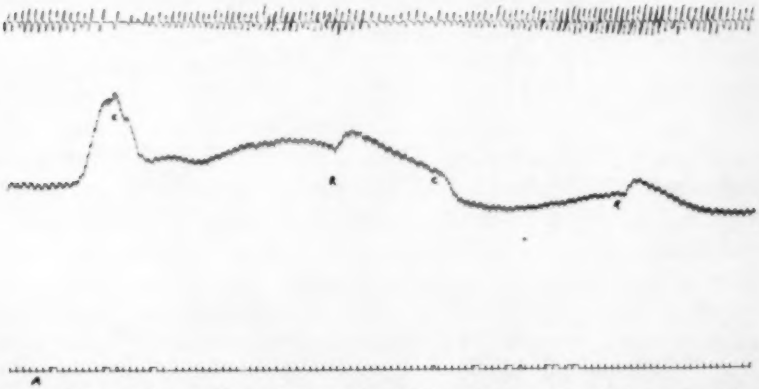

Fig. 5 (experiment 5).—One minim (0.06 cc.) of epinephrine was injected intravenously at *A*. The right pulmonary artery was occluded at the top of the epinephrine curve at *C* and released at *R*. It was clamped again on the fall of the epinephrine curve at *C* and released at *R*. Time in seconds.

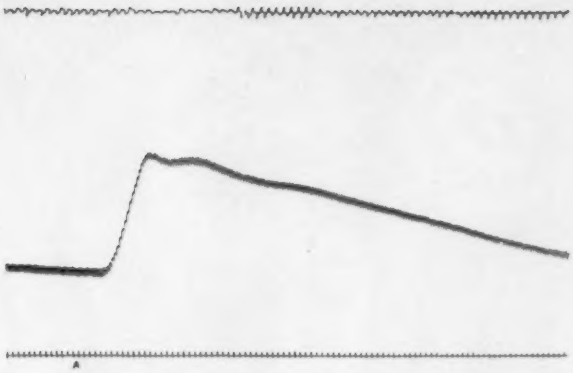

Fig. 6 (experiment 5).—The spinal cord was severed at the seventh cervical segment and 1 minim (0.06 cc.) of epinephrine was injected intravenously at *A*. This figure illustrates the epinephrine curve in a dog the spinal cord of which had been sectioned. Time in seconds.

Fig. 7 (experiment 13).—The spinal cord was sectioned at the seventh cervical segment, and the right pulmonary artery was occluded at *C* and released at *R*. Time in seconds.

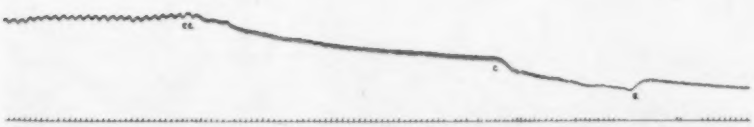

Fig. 8 (experiment 7).—The spinal cord was sectioned at the foramen magnum, and artificial respiration was given with a Masters pump. No record was made of the respirations. The cord was cut at *CC*, and the right pulmonary artery was occluded at *C* and released at *R*. Time in seconds.

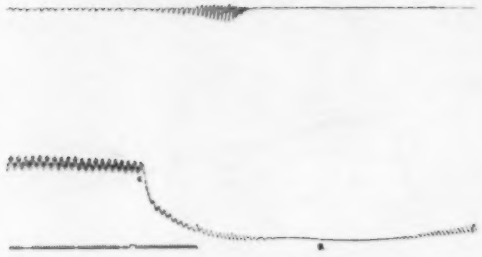

Fig. 9 (experiment 4).—The vagi and spinal cord were cut (seventh cervical segment). The right pulmonary artery was occluded at *C* and released at *R*. Time in seconds.

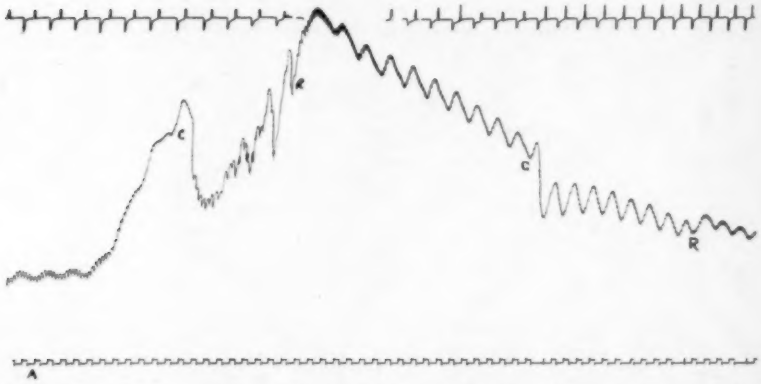

Fig. 10 (experiment 10).—The cord was sectioned at the seventh cervical segment, and the vagi were also cut. One minim (0.06 cc.) of epinephrine was given at *A*. The right pulmonary artery was occluded at *C* and released at *R*.

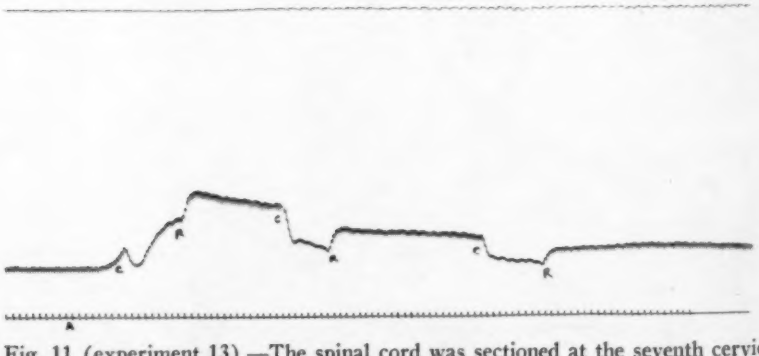

Fig. 11 (experiment 13).—The spinal cord was sectioned at the seventh cervical segment. One minim (0.06 cc.) of epinephrine was given intravenously at *A*, and the right pulmonary artery was occluded at *C* and released at *R*.

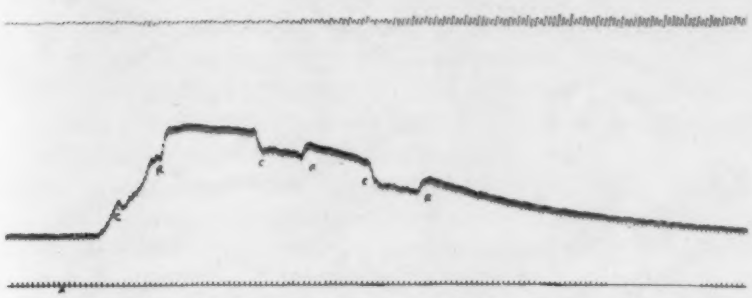

Fig. 12 (experiment 13).—The spinal cord was sectioned at the seventh cervical segment. Two minims (0.12 cc.) of epinephrine was given at *A*. The right pulmonary artery was occluded at *C* and released at *R*. In comparison with figure 11, the decrease in pressure at *C* was not as great, and the recovery between *C* and *R* was quicker on the rise of the epinephrine curve.

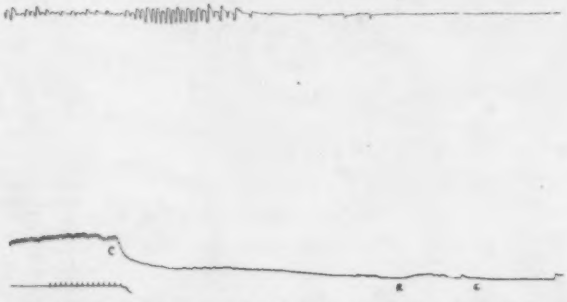

Fig. 13 (experiment 13).—The spinal cord was sectioned at the seventh cervical segment. The right pulmonary artery was occluded at *C* and released at *R*. Note the decrease in pressure with no tendency to recover.

COMMENT

It must be admitted that this problem cannot be definitely and conclusively proved beyond a question of doubt until it has been shown whether or not there is an increase or a decrease in the volume of blood passing through the unobstructed lung per minute after one branch of the pulmonary artery has been occluded in the closed chest. What happens to the capillary bed in the unobstructed lung is not definitely known, although it has been shown (Horine and Warner [12]) that there is a marked dilatation of the capillaries in the unligated lung as early as two hours after occlusion of a branch of the pulmonary artery. But this compensatory rise occurs within thirty seconds at most, and there are no anatomic data to indicate what changes may occur within so short a time.

Assuming that the initial decrease in the carotid pressure in the normal dog after occlusion of the right pulmonary artery is due to a

12. Horine, C. F., and Warner, C. G.: Experimental Occlusion of the Pulmonary Artery: An Anatomic Study, Arch. Surg., this issue, p. 139.

decrease in the output of the left ventricle, the compensatory rise in pressure is built up by an increase in the volume of blood passing through the remaining unobstructed lung per minute and then given to the left ventricle, by an increase in the peripheral resistance in the systemic circuit, by the ability of the muscle of the heart to increase the duration of systole to maintain or to increase that pressure, or by a combination of the aforementioned mechanisms.

A review of the literature shows that no experimental work has been done to determine the immediate volume of blood flowing through the unobstructed lung during the compensatory rise in pressure. Our

Observations on Dogs

Dog	Time for Maximum Decrease in Blood Pressure, Seconds	Amount of Maximum Decrease in Blood Pressure, Mm.	Time for Recovery of Blood Pressure to Normal, Seconds	Blood Pressure Curves	Respiration
1	4	12	14	Decrease in amplitude	Temporary slight decrease in amplitude
2	7	77	22	Decrease in rate and amplitude	Increase in rate and amplitude
3	3	11	20	Decrease in amplitude	No change
4	5	9	27	Decrease in amplitude	Slight temporary decrease in amplitude
5	3	19	13	Decrease in amplitude	Increase in rate and amplitude
6	3	28	30	Decrease in amplitude	Slight temporary decrease in amplitude
7	4	11	13	Decrease in amplitude	No change
8	4	18	13	Decrease in amplitude	Slight temporary decrease in amplitude
9	4	23	17		
10	4	26	9	Decrease in amplitude	Slight temporary decrease in amplitude
11	3	13	13	Decrease in amplitude	Temporary decrease in amplitude
12	7	36	14	Decrease in amplitude	Temporary decrease in amplitude
13	4	17	21	Decrease in amplitude	Temporary decrease in amplitude
Approximate average	4	23*	17		

* Approximate average 18 mm. if dog 2 is excluded.

experiments have shown that after the pressure has recovered from the initial fall, the release in the occluded vessel causes a still greater rise in pressure, which shows that the supply to the left ventricle has been enhanced. The second rise in pressure is more abrupt than the original compensatory curve in the same animal, and the recovery from the secondary rise to the normal base line consumes less time. From this one might infer that the original compensatory rise is not initiated by an increase in the volume of blood passing through the unobstructed lung in one minute.

When the cord has been sectioned, with a subsequent loss of tone in the peripheral capillary bed, the compensatory rise in pressure does not occur, but if epinephrine is given to restore a certain amount of the loss, the pressure curve regains its usual contour, as in the dog with the

intact vagus and intact spinal cord. Most authorities believe that epinephrine has very little or no effect directly on the muscle of the heart. Extensive experimental work shows that epinephrine increases the pulmonary resistance by causing a constriction of the pulmonary arteries.

The compensatory rise in the carotid pressure in the dog after the cord has been sectioned following occlusion of the right pulmonary artery occurs only during the phase when the epinephrine is active. On the fall of the epinephrine curve, a compensatory rise in pressure does not occur if the right pulmonary artery is occluded. This shows definitely that the vasoconstrictors play a great part in helping to maintain a normal pressure after sudden occlusion of a part of the pulmonary arterial tree. Perhaps this mechanism is followed by a sudden dilatation of the remaining pulmonary capillaries, with a subsequent increase in the volume of blood to be sent to the left side of the heart. If this is true, then death may be caused by the inability of the remaining capillaries of the lungs to dilate or by inability of the right side of the heart to pump the required amount of blood through the lungs to the left ventricle.

Clinically, death might be expected after occlusion of a portion of the pulmonary artery if this occurred in a patient who had decompensation of the right side of the heart, or in a person with low blood pressure, especially a fat person of the emphysematous type. These considerations should be kept in mind in selecting cases of various pulmonary conditions for radical treatment in which ligation of branches of the pulmonary artery is contemplated. The treatment may be preventative in the type of cases of unilateral pulmonary embolism about which we have spoken. When this acute accident occurs, immediate forceful circulatory stimulation may carry the patient over the period of circulatory collapse of the systemic system until the pulmonary system can increase the volume lost in the occluded lung.

CONCLUSIONS

1. Occlusion of a branch of the pulmonary artery causes a temporary decrease in the carotid blood pressure in the otherwise normal dog.

2. The recovery from the fall in the carotid blood pressure after occlusion of one half of the pulmonary artery requires from ten to thirty seconds.

3. Occlusion of one half of the pulmonary artery in a dog when the spinal cord has been sectioned causes death.

4. The vasoconstrictors of the sympathetic system play an important part in causing the compensatory rise in the carotid pressure after one half of the pulmonary artery has been occluded.

5. Occlusion of from 75 to 100 per cent of the pulmonary artery causes death.

RETURN OF GASTRIC ACIDITY AFTER SUBTOTAL GASTRECTOMY AND DOUBLE VAGOTOMY

PHILIP F. SHAPIRO, M.D.
AND
BENJAMIN N. BERG, M.D.
NEW YORK

One of the fundamental principles underlying the treatment of peptic ulcers is an attempt to control gastric acidity. This idea is based on the assumption that the presence of hydrochloric acid is an important contributory factor in the etiology of ulcers.[1] As a result, various surgical measures are employed to reduce the acidity of the gastric contents. Simple procedures, such as gastro-enterostomy [2] and pyloroplasty,[3] afford only a temporary neutralization of gastric acidity and the development of recurrences and jejunal ulcers after these operations is attributed largely to the persistence of hyperchlorhydria. In order to achieve more lasting cures subtotal gastrectomy is advocated [4] as a method which provides for a permanent lowering of gastric acidity by interfering with the normal mechanism of acid secretion.

According to the present concept of the physiology of the stomach, acid is secreted normally in four phases. The first is the cephalic phase

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A preliminary report of this work appeared in Proceedings of Society for Experimental Biology and Medicine (**29**:743, 1932).

From the Surgical Pathological Laboratory and the Department of Pathology, College of Physicians and Surgeons, Columbia University, and the Surgical Department of the Presbyterian Hospital.

1. Lindau, A., and Wulff, H.: The Peptic Genesis of Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **53**:621, 1932. Hauser, G.: Die peptischen Schädigungen des Magens, des Duodenums und der Speiseröhre und das peptische postoperative Jejunalgeschwür, in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 4.

2. Berberich, J.: Nach Untersuchungen von Gastroenterostomien wegen Ulcus ventriculi und Ulcus duodeni, unter besonderer Berücksichtigung der Röntgendiagnostik, Beitr. z. klin. Chir. **119**:194, 1932. Lewisohn, R., and Feldman, R. H.: Failure of Gastroenterostomy to Effect a Decisive Reduction in Gastric Acidity, Ann. Surg. **82**:925, 1925.

3. Finney, J. M., and Friedenwald, J.: Thirteen Years' Experience with Pyloroplasty, Surg., Gynec. & Obst. **18**:273, 1914.

4. Finsterer, H.: Die chirurgische Behandlung des Magens und Zwolffingerdarmgeschwüres und seiner Komplikationen, Ergebn. d. ges. Med. **15**:431, 1930-1931.

which is controlled by the vagi. This corresponds to the appetite juice or psychic secretion described originally by Pavlov [5] in dogs and later by Carlson [6] in man. In the second or gastric phase, mechanical and chemical stimuli and secretagogues derived from food excite secretion.[7] In addition, according to Edkins,[8] during this phase a hormone, "gastrin," is liberated by the antrum and pylorus which stimulates the secretion of acid by the glands of the fundus. However, the existence of a specific gastric hormone is doubtful.[9] In the third or intestinal phase gastric secretion is prolonged by reflex stimuli originating [10] in the small intestine during the process of digestion. The fourth phase is the period of interdigestive, basal or continuous secretion. This secretion is probably a manifestation of vagus activity.[11]

From the surgical standpoint it is impossible to exclude the intestinal and continuous phases, but the first and second periods are amenable to modification. Attempts to reduce the psychic phase by dividing the vagi above or below the diaphragm have been unsuccessful. In dogs, Hartzell [12] found a reduction in acid after supraphrenic double vagotomy, but two years later Vanzant,[13] working with the same animals, reported that the acid had returned to normal values. Others [14] have

5. Pavlov, L. P.: The Work of the Digestive Glands, London, Griffin & Company, 1910, p. 101.

6. Carlson, A. J.: The Control of Hunger in Health and Disease, Chicago, University of Chicago Press, 1916, p. 235.

7. (*a*) Ivy, A. C.: Rôle of Hormones in Digestion, Physiol. Rev. **10**:282, 1930. (*b*) Lim, R.; Ivy, A. C., and McCarthy, J. E.: Gastric Secretion by Local Stimulation, Quart. J. Exper. Physiol. **15**:12, 1925. (*c*) Sawitsch, W., and Zeljony, G.: Zur Physiologie des Pylorus, Arch. f. d. ges. Physiol. **150**:128, 1913.

8. Edkins, J. S.: The Chemical Mechanism of Gastric Secretion, J. Physiol. **34**:133, 1906.

9. (*a*) Ivy.[7a] (*b*) Tomaszewski, Z.: Ueber die chemischen Erreger der Magendrüsen, Arch. f. d. ges. Physiol. **170**:260, 1918; **171**:1, 1918. (*c*) Priestley, J. T., and Mann, F. C.: Gastric Acidity with Special Reference to the Pars Pylorica and Pyloric Mucosa: An Experimental Study, Arch. Surg. **25**:395 (Aug.) 1932.

10. Ivy, A. C.: The Intestinal Phase of Gastric Secretion, Quart. J. Exper. Physiol. **15**:55, 1925.

11. Carlson,[6] p. 245.

12. Hartzell, J. B.: The Effect of Vagus Section on Gastric Acidity, Am. J. Physiol. **91**:161, 1929.

13. Vanzant, F. R.: Late Effects of Section of Vagus Nerves on Gastric Acidity, Am. J. Physiol. **99**:375, 1932.

14. (*a*) McCrea, E. D.; McSwiney, B. A., and Stopford, J. S.: The Effect on the Stomach of Section of the Vagus Nerves, Quart. J. Exper. Physiol. **16**:195, 1926. (*b*) Kuntz, A.: The Autonomic Nervous System, Philadelphia, Lea & Febiger, 1929, p. 216. (*c*) Friedenwald, J., and Feldman, M.: Experimental Studies on the Effect of Section of the Vagus Nerve on Gastric Secretion, Arch. Int. Med. **49**:234 (Feb.) 1932.

also observed the return of gastric acidity after section of the vagi in animals. In man[15] division of one or both vagi produces only a transient decrease in gastric acidity.

Various types of operations on the stomach have been devised with the purpose of altering the second phase of gastric secretion. Side-tracking procedures and pyloroplasties have only a transient effect, which depends largely on the degree of neutralization of the gastric contents by regurgitated intestinal fluids. The more radical operation of subtotal gastrectomy aims to eliminate the second phase by removing the so-called hormone-elaborating portion of the stomach (antrum and pylorus). This is an effort directed toward modification of the mechanism of gastric secretion rather than simple neutralization of acidity.

The results of a number of experimental investigations in dogs indicate that resection of the pylorus and antrum has no permanent influence on gastric acidity. Smidt[16] studied the secretions obtained from Pavlov pouches in dogs after the Billroth I and II types of gastric resections. He found that the amount of secretion was diminished and the duration of the response to a test meal shortened, and ascribed this result to the absence of the second phase. However, the percentage of hydrochloric acid remained practically unchanged. In his conclusions he stated that it was impossible to attain complete "anacidity," owing to the fact that the psychic phase and reflex secretion remained unaffected. Enderlen and Zuckschwerdt,[17] having observed high acid values in the gastric contents of two patients many years after radical resection of the stomach, repeated Smidt's experiments, and studied the secretions from the pouches for longer periods of time. After four months their results were similar to those reported by Smidt. However, one year afterward the same animals showed a complete return of the second phase. As a matter of fact, frequently the quantity of secretion was greater and the duration of the response was longer than before resection. Again the percentage of hydrochloric acid was unchanged. They concluded that removal of the pylorus disturbed temporarily the second phase of secretion, but that a readjustment took place whereby the small intestine took over the function

15. Pieri, G., and Tanferna, U.: Effetti della resezione del vago sulla secrezione gastrica dell'uomo, Riforma med. **46**:323, 1930.

16. Smidt, H.: Experimentelle Studien am nach Pawlow isolierten kleinen Magen, über die sekretorisch Arbeit der Magendrüsen nach den Resektionen Billroth I und II, sowie nach der Pylorusausschaltung nach von Eiselsberg, Arch. f. klin. Chir. **125**:26, 1923.

17. Enderlen, E., and Zuckschwerdt, L.: Die Erregung der Magensaftsekretion nach Resektion des Antrum-Pylorusteils des Magens, Deutsche Ztschr. f. Chir. **232**:290, 1931.

of the pylorus as the stimulus for secretion by the fundus. London [18] found a temporary depression in gastric acidity after removal of the antrum and pylorus in dogs, and attributed the result to neutralization by regurgitated alkaline duodenal secretions. One month after resection he noted that the acidity of the gastric contents had returned to normal values, and reexamination of the same animals one year and three years later revealed that the chemistry of the gastric secretions was unaltered. In his animals, jejunal ulcers occurred practically always at the site of anastomosis between the fundus and jejunum. Portis and Portis [19] studied gastric secretion for several months after subtotal gastrectomy in dogs with Pavlov pouches. These investigators found no appreciable changes in the acidity of the secretion obtained from the pouch; in the main stomach no free hydrochloric acid was present, owing to neutralization by intestinal fluids, but the combined acidity was high. Recently, Priestley and Mann [9c] reported no change in gastric acidity after extirpation of the pars pylorica, and found no evidence of a humoral mechanism originating in the pyloric mucosa in dogs equipped with pyloric and totally transplanted fundic pouches.

In man, the results of investigations concerning gastric secretion after subtotal resection are difficult to interpret and inconclusive, owing to the unsatisfactory manner in which the studies have been conducted.[20] The reports [21] are based on the results obtained from a single gastric analysis after the administration of a test meal. Often the type of test meal and the time of extraction are not recorded. As a rule, the interval between the operation and the estimation of gastric acidity is not mentioned. The motility of the fundic remnant, the position of the tip of the aspiration tube as observed by fluoroscopy and the amount of regurgitation as determined by the presence of bile and pancreatic

18. London, E. S.: Experimentelle Physiologie und Pathologie der Verdauung, Berlin, Urban & Schwarzenberg, 1925, p. 157.

19. Portis, S. A., and Portis, B.: Effects of Subtotal Gastrectomy on Gastric Secretion, J. A. M. A. **86**:836 (March 20) 1926.

20. (*a*) Katsch, G.: Pathologische Physiologie des Magensaftes und des Magenchemismus, in Bethe, A., and others: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1927, vol. 3, p. 1118. (*b*) Goetze, O.: Die Motilität und Sekretion des operierten Magens, in Bethe, A., and others: Handbuch der normalen und pathologischen Physiologie, vol. 3, p. 1199.

21. Schur, H., and Plaschkes, G.: Die Bedeutung der Funktion des Antrum pylori für die Magen Chirurgie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **28**:795, 1914-1915. Lorenz, H., and Schur, H.: Unsere Erfahrungen über den Wert der Antrumresektion bei der Behandlung des Ulcus pepticum, Arch. f. klin. Chir. **119**: 219, 1922. Smidt, H.: Ueber Magenresektion und Magenchemismus, ibid. **130**: 307, 1924. Lewisohn, R., and Ginzburg, L.: Relation of Post-Operative Achlorhydria to Cure of Gastric and Duodenal Ulcers, Surg., Gynec. & Obst. **47**:493, 1928. Louria, H. W.: The Surgical Treatment of Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **47**:493, 1928.

enzymes in the gastric contents are details which are disregarded. Hence, the reports of "anacidity" after subtotal gastrectomy cannot be accepted without further, more complete studies. Klein [22] compared the acidity of the gastric contents following an Ewald meal, extracted after three quarters of an hour, with the acidity values following a Rehfuss meal, removed at frequent intervals during a period of three hours, in the same patient after subtotal removal of the stomach. In many instances he found that free acid appeared only after the first hour and then increased in amount in the succeeding specimens, demonstrating that acid values based on a single analysis after an Ewald meal are inadequate. Using the fractional method of analsyis, Klein reported that six months after gastric resection for duodenal ulcer 25 per cent of the patients showed anacidity (absence of free hydrochloric acid), 41 per cent hypo-acidity and 17 per cent hyperacidity. For the last group of cases with intractable hyperacidity he suggested division of the left vagus [23] in an attempt to eliminate the psychic phase and possibly the phase of continuous secretion which he believed to be the underlying factors in the failure to reduce acidity after subtotal gastrectomy. In a preliminary communication he reported anacidity in eight patients from two to six months after vagotomy. Goetze [20b] attributed the high acid values which were encountered in man, even after extensive gastric resections, to the influence of unalterable reflex stimuli.

According to Finsterer,[24] von Haberer [25] and Berg,[26] the increasing number of recurrences and jejunal ulcers which are being reported [27] after subtotal gastrectomy are due principally to inadequate removal of the stomach and persistent hyperacidity. In order to overcome the

22. Klein, E.: Gastric Secretion After Partial Gastrectomy, J. A. M. A. **89**: 1235 (Oct. 8) 1927.

23. Klein, E.: Left Vagus Section and Partial Gastrectomy for Duodenal Ulcer with Hyperacidity, Ann. Surg. **90**:65, 1929.

24. Finsterer, H.: Beziehungen zwischen grösse der Magenresektion und Dauerheilung bei der Ulcus-Behandlung, Beitr. z. klin. Chir. **147**:78, 1927.

25. von Haberer, H.: Betrachtungen über Misserfolge nach Resektion wegen Magen und Duodenalgeschwüren, Zentralbl. f. Chir. **57**:66, 1930; Resektion zur Ausschaltung und rezidivierendes Jejunalucus, Arch. f. klin. Chir. **146**:651, 1927.

26. Berg, A. A.: Mortality and Late Results of Subtotal Gastrectomy for Radical Cure of Gastric and Duodenal Ulcer, Ann. Surg. **92**:340, 1930.

27. Birgfeld, E.: Ulcus pepticum jejuni nach Magenresektion, Arch. f. klin. Chir. **137**:568, 1925. Balfour, D. C.: Recurring Ulcers Following Partial Gastrectomy, Ann. Surg. **88**:548, 1928. Hurst, A.: The Later Results of Partial Gastrectomy for Gastric and Duodenal Ulcer, Lancet **2**:680, 1928. Moynihan, B.: Some Problems in Gastric Surgery, Brit. M. J. **2**:1021, 1928. Starlinger, F.: Das Rückfallsgeschwür nach Magenresektion wegen Ulcus ventriculi oder duodeni, Arch. f. klin. Chir. **162**:564, 1930. Jaeger, F.: Ueber die Ulcusrezidive nach Magenresektion, Arch. f. klin. Chir. **161**:233, 1930.

hyperacidity of peptic ulcers and produce a permanent decrease in the output of hydrochloric acid, Finsterer [4] advocates the resection of at least two thirds of the stomach, so that a large area of secretory mucosa of the fundus is removed as well as the antrum and pylorus.

In view of the incomplete knowledge concerning the etiology of peptic ulcers in man, the necessity of lowering the acidity of the gastric juice in order to accomplish a cure is still open to question. As an example of the beneficial effects which may be secured without altering gastric acidity, the recent good results with mucin therapy may be cited. Brown and his co-workers [28] reported that the administration of mucin to patients with intractable ulcers results in marked improvement. They found that mucin in ordinary doses does not diminish gastric acidity appreciably when placed in the stomach after a two hour fractional test meal, followed by aspirations at frequent intervals of from four to seven hours.

Since significant changes in gastric acidity depend essentially on alterations in gastric secretion, the following investigation was undertaken in order to determine experimentally to what extent the secretory mechanism of the stomach can be modified by surgical intervention. The operation of subtotal gastrectomy and double vagotomy was chosen for this purpose, being considered the most radical procedure which could be employed surgically to alter the different phases of gastric secretion.

METHODS

Complete studies were made on eight dogs. All operations were performed under ether anesthesia and with strict asepsis. First, in order to observe gastric secretory activity unmodified by such factors as food, abnormal motility and intestinal regurgitation, a pouch derived entirely from the fundus of the stomach was constructed according to the technic described by Pavlov.[29] It is important to remember that the innervation of a Pavlov pouch remains intact. Then, from three to four weeks later, a subtotal gastrectomy was performed according to the Pólya [30] method and both vagi were divided. The distal two thirds of the stomach was resected beginning 3 cm. or more proximal to the incisura angularis and extending well beyond the pylorus. After closing the stump of the duodenum an end-to-side suture gastro-jejunostomy was done to reestablish the continuity of the stomach and small intestine. In order to determine whether the antrum and pylorus were removed completely, histologic examinations of the resected specimens and fundic remnants were made. It was found that although the site of demarcation between pyloric and fundic glands was variable in different animals, the resections were always carried well beyond the zone of transition, into the fundus.

28. Brown, C. F. G.; Cramer, S. P.; Jenkinson, E. L., and Gilbert, N. C.: Mucin Therapy for Peptic Ulcer, J. A. M. A. **99**:98 (July 9) 1932.

29. Pavlov,[5] p. 13.

30. Pólya, E.: Zur Stumpfversorgung nach Magenresektion, Zentralbl. f. Chir. **38**:892, 1911.

The anterior and posterior vagi were isolated on the abdominal portion of the esophagus and divided. In addition, the entire circumference of the esophagus was dissected free from all nerve filaments in order to insure complete interruption of smaller branches of the vagi. This was confirmed later at autopsy. Several anatomic dissections of the vagi were made, and the abdominal distribution of the nerves corresponded to McCrea's description.[31] At the lower end of the thoracic esophagus the right and left vagi break up into plexuses from which they emerge as two main trunks, an anterior and a posterior one. The nerves then pass through the esophageal opening in the diaphragm as two trunks, occasionally as three, rarely as four, and send their branches to the anterior and posterior surfaces of the stomach.

Gastric secretion was studied in the following manner. After the animals had been deprived of food for twenty-four hours, the fasting contents were aspirated. Then a test meal, consisting of from 100 to 150 Gm. of lean meat and 250 cc. of water, was given. Specimens were aspirated for analysis at hourly intervals for periods extending from four to seven hours after the administration of the test meal; the pouch was emptied of its contents each time but only samples sufficient for examination were withdrawn from the main stomach. Although there were individual variations in the secretory rates of different animals, there was a rough parallelism between the curve of acidity and the rate of secretion in the pouch of each dog before and after resection-vagotomy. This conformed with the previous observations of Pavlov,[32] Hollander and Cowgill [32a] and Portis and Portis.[19] As a rule, 10 cc. of juice was employed for titration; if this amount was not available, 5 cc. was used. Free, combined and total acid were determined in clinical units by titrating against tenth-normal sodium hydroxide, using Töpfer's reagent and phenolphthalein as indicators. Since in our experiments the hydrochloric acid was present principally as free acid in the pouch and in combination with proteins derived from meat and mucus in the main stomach, it was desirable for the sake of uniformity and simplicity to express the secretory activity of both by a common measure. For this purpose the value for total acidity was found to be most practical because the curves of acidity in the pouch and main stomach tended to run parallel to one another (see experimental results and charts). The gastric analyses were conducted in three stages: First, as a control, the response of the intact stomach to the test meal was established before any operative intervention. Then the acidity of the secretions of the pouch and main stomach was determined, usually from two to three weeks after the construction of the pouch. Finally, the secretory activity of the pouch and fundic remnant was observed within from five to seventeen days after resection-vagotomy and at frequent intervals afterward for periods extending from eight to twelve weeks.

In order to study vagus activity before and after double vagotomy, 2 mg. of atropine was injected subcutaneously at the time a test meal was given and a gastric analysis was made in the usual manner, the results being compared.

EXPERIMENTAL RESULTS

The accompanying tables and charts represent the results which were obtained in the eight experiments.

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31. McCrea, E. D.: The Abdominal Distribution of the Vagus, J. Anat. **59**:18, 1924.

32. Pavlov,[5] p. 33.

32a. Hollander, F., and Cowgill, G. R.: Studies in Gastric Secretion, J. Biol. Chem. **91**:151, 1931.

TABLE 1.—*Results of Test Meals in Dog 6; Acidity in Clinical Units*

A. Before Operation

	Stomach		
	Free	Combined	Total
Fasting	8	14	22
1 hour	0	102	102
2 hours	0	110	110
3 hours	8	82	90
4 hours	30	30	60
5 hours	10	16	26

B. After Formation of Pavlov Pouch, Before Resection-Vagotomy

	Pouch			Stomach		
	Free	Combined	Total	Free	Combined	Total
Fasting	22	12	34	0	28	28
1 hour	122	12	134	0	96	96
2 hours	130	10	140	0	106	106
3 hours	112	10	122	18	54	72
4 hours	80	12	92	12	43	55
5 hours	34	16	50	0	24	24

2 Mg. of Atropine Before Resection-Vagotomy

Fasting	20	12	32	0	20	20
1 hour	34	10	44	0	30	30
2 hours	12	12	24	0	22	22
3 hours	10	16	26	0	24	24
4 hours	44	14	58	10	38	48
5 hours	86	10	96	25	20	45
6 hours	115	10	125	16	18	34

C. 7 Days After Resection-Vagotomy

Fasting	0	12	12	0	12	12
1 hour	26	10	36	0	30	30
2 hours	38	8	46	0	34	34
3 hours	18	10	28	0	20	20
4 hours	4	12	16	0	10	10

12 Days After Resection-Vagotomy

	Pouch			Stomach		
	Free	Combined	Total	Free	Combined	Total
Fasting	0	8	8	0	10	10
1 hour	50	8	58	0	52	52
2 hours	76	8	84	0	70	70
3 hours	48	10	58	0	50	50
4 hours	12	18	30	0	16	16

33 Days After Resection-Vagotomy

Fasting	12	12	24	0	16	16
1 hour	100	10	110	0	80	80
2 hours	126	8	134	0	92	92
3 hours	90	12	102	0	60	60
4 hours	52	14	66	8	30	38
5 hours	18	14	32	4	16	20

2 Mg. of Atropine 34 Days After Resection-Vagotomy

Fasting	16	10	26	0	18	18
1 hour	22	12	34	0	24	24
2 hours	10	12	22	0	16	16
3 hours	10	14	24	0	32	32
4 hours	48	12	60	10	42	52
5 hours	82	12	94	15	30	45
6 hours	108	12	120	12	20	32
7 hours	100	14	114	0	16	16

57 Days After Resection-Vagotomy

Fasting	18	12	30	0	14	14
1 hour	118	8	126	0	102	102
2 hours	130	8	138	0	108	108
3 hours	118	6	124	0	62	62
4 hours	84	10	94	12	32	44
5 hours	32	14	46	10	12	22

TABLE 2.—*Results of Test Meals in Dog 8; Acidity in Clinical Units*

A. Before Operation

	Stomach		
	Free	Combined	Total
Fasting	0	16	16
1 hour	0	58	58
2 hours	0	82	82
3 hours	12	32	44
4 hours	0	14	14

B. After Formation of Pavlov Pouch, Before Resection-Vagotomy

	Pouch			Stomach		
	Free	Combined	Total	Free	Combined	Total
Fasting	24	12	36	0	24	24
1 hour	90	8	98	0	52	52
2 hours	100	8	108	0	86	86
3 hours	78	10	88	12	28	40
4 hours	60	10	70	24	10	34
5 hours	38	12	50	0	12	12

2 Mg. of Atropine Before Resection-Vagotomy

Fasting	30	14	44	0	22	22
1 hour	6	18	24	0	16	16
2 hours	28	12	40	0	24	24
3 hours	40	10	50	0	54	54
4 hours	100	10	110	0	60	60
5 hours	70	12	82	0	42	42
6 hours	30	14	44	0	18	18

C. 12 Days After Resection-Vagotomy

Fasting	16	14	30	0	14	14
1 hour	48	10	58	0	36	36
2 hours	44	12	56	0	38	38
3 hours	26	12	38	0	26	26
4 hours	52	10	62	0	30	30
5 hours	70	10	80	10	20	30

26 Days After Resection-Vagotomy

	Pouch			Stomach		
	Free	Combined	Total	Free	Combined	Total
Fasting	8	12	20	0	12	12
1 hour	92	10	102	0	40	40
2 hours	94	10	104	0	52	52
3 hours	65	10	75	10	20	30
4 hours	40	12	52	0	18	18
5 hours	70	12	82	10	12	22
6 hours	88	10	98	6	14	20

2 Mg. of Atropine, 27 Days After Resection-Vagotomy

Fasting	0	12	12	0	10	10
1 hour	0	8	8	0	8	8
2 hours	14	10	24	0	18	18
3 hours	34	10	44	0	36	36
4 hours	66	10	76	0	46	46
5 hours	97	8	105	6	34	40
6 hours	68	8	76	0	16	16
7 hours	50	10	60			

60 Days After Resection-Vagotomy

Fasting	0	12	12	0	10	10
1 hour	93	7	100	0	50	50
2 hours	100	8	108	4	52	56
3 hours	84	8	92	0	30	30
4 hours	80	6	86	0	32	32
5 hours	60	8	68	0	12	12
6 hours	110	6	116	0	18	18
7 hours	90	8	98	0	14	14
8 hours	38	10	48			

Two penetrating jejunal ulcers. One of them perforated, but was sealed by the tip of the quadrate lobe of the liver

TABLE 3.—*Results of Test Meals in Dog 1; Acidity in Clinical Units*

A. Before Operation

	Stomach		
	Free	Combined	Total
Fasting	0	10	10
1 hour	0	60	60
2 hours	18	82	100
3 hours	34	48	82
4 hours	20	42	62

B. After Formation of Pavlov Pouch, Before Resection-Vagotomy

	Pouch			Stomach		
	Free	Combined	Total	Free	Combined	Total
Fasting	0	8	8	0	12	12
1 hour	64	6	70	0	52	52
2 hours	110	4	114	14	80	94
3 hours	94	10	104	30	49	79
4 hours	69	12	81	18	46	64

C. 12 Days After Resection-Vagotomy

Fasting	7	8	15	0	12	12
1 hour	14	8	22	0	19	19
2 hours	43	13	56	0	36	36
3 hours	50	12	62	0	30	30
4 hours	45	15	60	0	28	28

33 Days After Resection-Vagotomy

Fasting	5	16	21	4	20	24
1 hour	20	16	36	0	38	38
2 hours	32	14	46	0	52	52
3 hours	38	18	56	0	56	56
4 hours	52	16	68	6	54	60
5 hours	68	16	84	8	34	42

54 Days After Resection-Vagotomy

	Pouch			Stomach		
	Free	Combined	Total	Free	Combined	Total
Fasting	22	14	36	0	22	22
1 hour	36	14	50	0	38	38
2 hours	54	14	68	0	52	52
3 hours	96	12	108	0	72	72
4 hours	120	14	134	12	86	98
5 hours	115	10	125	10	70	80
6 hours	96	14	110	8	44	52

2 Mg. of Atropine, 56 Days After Resection-Vagotomy

Fasting	12	12	24	0	18	18
1 hour	0	10	10	0	10	10
2 hours	14	14	28	0	22	22
3 hours	34	14	48	0	42	42
4 hours	85	13	98	0	68	68
5 hours	94	12	106	10	80	90
6 hours	64	16	80	0	72	72

68 Days After Resection-Vagotomy

Fasting	8	12	20	0	22	22
1 hour	36	14	50	0	36	36
2 hours	58	16	74	0	66	66
3 hours	92	12	104	0	84	84
4 hours	112	12	124	10	88	98
5 hours	92	10	102	18	48	66
6 hours	42	12	54	10	30	40

84 Days After Resection-Vagotomy

Fasting	12	12	24	0	24	24
1 hour	40	12	52	0	50	50
2 hours	64	14	78	0	80	80
3 hours	98	10	108	0	96	96
4 hours	116	8	124	12	73	95
5 hours	107	8	115	20	30	50
6 hours	81	14	95	8	20	28

TABLE 4.—*Results of Test Meals in Dog 2; Acidity in Clinical Units*

A. Before Operation

	Stomach		
	Free	Combined	Total
Fasting	0	12	12
1 hour	0	85	85
2 hours	0	92	92
3 hours	0	90	90
4 hours	8	56	64
5 hours	26	14	40

B. After Formation of Pavlov Pouch, Before Resection-Vagotomy

	Pouch			Stomach		
	Free	Combined	Total	Free	Combined	Total
Fasting	0	16	16	0	12	12
1 hour	104	8	112	0	82	82
2 hours	108	10	118	0	94	94
3 hours	86	10	96	22	66	88
4 hours	48	12	60	30	24	54
5 hours	20	14	34	12	16	28

2 Mg. of Atropine Before Resection-Vagotomy

Fasting	16	16	32	0	22	22
1 hour	24	10	34	0	30	30
2 hours	40	10	50	0	38	38
3 hours	38	12	50	0	32	32
4 hours	28	14	42	0	20	20
5 hours	85	12	97	24	16	40
6 hours	95	10	105	38	16	54

C. 12 Days After Resection-Vagotomy

Fasting	0	12	12	0	10	10
1 hour	64	10	74	0	44	44
2 hours	75	10	85	0	58	58
3 hours	72	8	80	0	52	52
4 hours	54	10	64	0	35	35
5 hours	8	16	24	0	12	12

33 Days After Resection-Vagotomy

	Pouch			Stomach		
	Free	Combined	Total	Free	Combined	Total
Fasting	22	10	32	0	20	20
1 hour	116	8	124	0	84	84
2 hours	122	8	130	0	90	90
3 hours	118	10	128	18	58	76
4 hours	86	14	100	10	38	48
5 hours	36	14	50	4	16	20

2 Mg. of Atropine, 34 Days After Resection-Vagotomy

Fasting	8	14	22	0	14	14
1 hour	16	10	26	0	18	18
2 hours	34	10	44	0	30	30
3 hours	33	12	45	0	34	34
4 hours	24	14	38	0	30	30
5 hours	84	10	94	10	50	60
6 hours	100	8	108	12	26	38
7 hours	70	10	80			

54 Days After Resection-Vagotomy

Fasting	10	14	24	0	12	12
1 hour	116	8	124	0	80	80
2 hours	125	5	130	0	90	90
3 hours	104	6	110	14	60	74
4 hours	54	8	62	16	24	40
5 hours	20	10	30	0	16	16

TABLE 5.—*Results of Test Meals in Dog 3; Acidity in Clinical Units*

A. Before Operation

	Stomach		
	Free	Combined	Total
Fasting	0	12	12
1 hour	0	74	74
2 hours	0	92	92
3 hours	14	28	42
4 hours	18	12	30

B. After Formation of Pavlov Pouch, Before Resection-Vagotomy

	Pouch			Stomach		
	Free	Combined	Total	Free	Combined	Total
Fasting	24	12	36	0	18	18
1 hour	90	8	98	0	70	70
2 hours	92	10	102	0	86	86
3 hours	58	12	70	8	32	40
4 hours	36	16	52	18	16	34

2 Mg. of Atropine Before Resection-Vagotomy

Fasting	14	14	28	0	20	20
1 hour	0	6	6	0	12	12
2 hours	0	4	4	0	12	12
3 hours	6	18	24	0	20	20
4 hours	36	16	52	8	42	50

C. 12 Days After Resection-Vagotomy

Fasting	0	6	6	0	10	10
1 hour	10	12	22	0	26	26
2 hours	22	14	36	0	38	38
3 hours	16	14	30	0	26	26
4 hours	0	14	14	0	14	14

26 Days After Resection-Vagotomy

Fasting	6	8	14	0	12	12
1 hour	30	10	40	0	36	36
2 hours	38	12	50	0	46	46
3 hours	32	14	46	8	34	42
4 hours	12	14	26	0	16	16
5 hours	6	16	22	0	12	12

33 Days After Resection-Vagotomy

	Pouch			Stomach		
	Free	Combined	Total	Free	Combined	Total
Fasting	10	10	20	0	14	14
1 hour	76	12	88	0	62	62
2 hours	96	14	110	0	74	74
3 hours	82	12	94	0	82	82
4 hours	66	12	78	10	58	68
5 hours	32	12	44	8	40	48

2 Mg. of Atropine, 35 Days After Resection-Vagotomy

Fasting	16	10	26	0	20	20
1 hour	6	14	20	0	16	16
2 hours	10	12	22	0	20	20
3 hours	30	12	42	0	30	30
4 hours	41	14	55	0	48	48
5 hours	50	17	67			

47 Days After Resection-Vagotomy

Fasting	0	12	12	0	16	16
1 hour	81	14	95	0	60	60
2 hours	92	14	106	0	92	92
3 hours	80	10	90	6	66	72
4 hours	32	12	44	10	38	48
5 hours	20	14	34	10	16	26

59 Days After Resection-Vagotomy

Fasting	14	12	26	0	20	20
1 hour	92	10	102	0	66	66
2 hours	98	8	106	0	96	96
3 hours	78	12	90	12	66	78
4 hours	42	14	56	10	42	52
5 hours	14	14	28	8	20	28

On the sixty-third day generalized peritonitis developed from perforated jejunal ulcers

TABLE 6.—*Results of Test Meals in Dog 4; Acidity in Clinical Units*

A. Before Operation

	Stomach		
	Free	Combined	Total
Fasting	0	14	14
1 hour	0	64	64
2 hours	0	96	96
3 hours	0	65	65
4 hours	20	18	38

B. After Formation of Pavlov Pouch, Before Resection-Vagotomy

	Pouch			Stomach		
	Free	Combined	Total	Free	Combined	Total
Fasting	28	10	38	0	16	16
1 hour	82	8	90	0	62	62
2 hours	112	12	124	0	94	94
3 hours	100	10	110	0	68	68
4 hours	70	12	82	16	30	46
5 hours	42	12	54	10	14	24
6 hours	30	10	40	0	14	14

2 Mg. of Atropine Before Resection-Vagotomy

Fasting	32	12	44	0	26	26
1 hour	20	10	30	0	16	16
2 hours	4	8	12	0	14	14
3 hours	32	10	42	0	40	40
4 hours	72	10	82	0	66	66
5 hours	84	10	94	16	76	92
6 hours	92	8	100	24	74	98
7 hours	32	12	44	0	22	22

C. 17 Days After Resection-Vagotomy

Fasting	0	18	18	0	10	10
1 hour	12	16	28	0	20	20
2 hours	22	16	38	0	32	32
3 hours	32	14	46	0	40	40
4 hours	36	14	50	0	30	30
5 hours	14	12	26	0	16	16

31 Days After Resection-Vagotomy

	Pouch			Stomach		
	Free	Combined	Total	Free	Combined	Total
Fasting	10	16	26	0	18	18
1 hour	24	12	36	0	32	32
2 hours	52	12	64	0	58	58
3 hours	60	14	74	10	60	70
4 hours	72	16	88	8	38	46
5 hours	48	14	62	0	22	22

45 Days After Resection-Vagotomy

Fasting	8	16	24	0	24	24
1 hour	46	14	60	0	60	60
2 hours	82	16	98	0	82	82
3 hours	100	10	110	10	82	92
4 hours	102	12	114	12	52	64
5 hours	72	18	90	0	18	18

2 Mg. of Atropine, 47 Days After Resection-Vagotomy

Fasting	16	14	30	0	20	20
1 hour	12	12	24	0	16	16
2 hours	8	12	20	0	14	14
3 hours	14	16	30	0	34	34
4 hours	56	10	66	0	60	60
5 hours	96	14	110	0	80	80

60 Days After Resection-Vagotomy

Fasting	0	18	18	0	22	22
1 hour	64	16	80	0	66	66
2 hours	94	14	108	0	90	90
3 hours	104	18	122	6	94	100
4 hours	112	14	126	12	70	82
5 hours	76	14	90	0	30	30
6 hours	34	12	46			

TABLE 7.—*Results of Test Meals in Dog 5; Acidity in Clinical Units*

A. Before Operation

	Stomach		
	Free	Combined	Total
Fasting	4	10	14
1 hour	0	85	85
2 hours	26	42	68
3 hours	26	20	46
4 hours	8	15	23

B. After Formation of Pavlov Pouch, Before Resection-Vagotomy

	Pouch			Stomach		
	Free	Combined	Total	Free	Combined	Total
Fasting	4	8	12	8	8	16
1 hour	12	15	27	0	82	82
2 hours	24	18	42	28	32	60
3 hours	6	12	18	20	26	46
4 hours	0	8	8	6	12	18

C. 5 Days After Resection-Vagotomy

Fasting	6	8	14	0	8	8
1 hour	20	10	30	0	42	42
2 hours	4	8	12	0	18	18
3 hours	0	10	10	0	13	13
4 hours	0	10	10	0	8	8

12 Days After Resection-Vagotomy

	Pouch			Stomach		
	Free	Combined	Total	Free	Combined	Total
Fasting	0	12	12	0	8	8
1 hour	22	13	35	5	65	70
2 hours	30	22	52	8	48	56
3 hours	39	20	59	0	18	18
4 hours	35	17	52	0	14	14

19 Days After Resection-Vagotomy

Fasting	20	18	38	0	26	26
1 hour	40	14	54	5	70	75
2 hours	60	15	75	6	45	51
3 hours	64	18	82	0	21	21
4 hours	32	10	42	0	20	20

2 Mg. of Atropine, 23 Days After Resection-Vagotomy

Fasting	39	6	45	0	25	25
1 hour	0	18	18	0	23	23
2 hours	0	23	23	0	32	32
3 hours	4	25	29	0	40	40
4 hours	60	22	82	0	75	75
5 hours	35	25	60	0	45	45

TABLE 8.—*Results of Test Meals in Dog 7; Acidity in Clinical Units*

A. Before Operation

	Stomach		
	Free	Combined	Total
Fasting	0	12	12
1 hour	0	72	72
2 hours	0	104	104
3 hours	18	46	64
4 hours	0	32	32

B. After Formation of Pavlov Pouch, Before Resection-Vagotomy

	Pouch			Stomach		
	Free	Combined	Total	Free	Combined	Total
Fasting	0	6	6	0	8	8
1 hour	100	12	112	0	64	64
2 hours	120	10	130	0	112	112
3 hours	94	16	110	15	60	75
4 hours	72	16	88	0	32	32
5 hours	24	18	42			

2 Mg. of Atropine Before Resection-Vagotomy

Fasting	8	10	18	0	12	12
1 hour	26	14	40	0	24	24
2 hours	12	20	32	0	18	18
3 hours	0	16	16	0	14	14
4 hours	0	22	22	0	28	28
5 hours	68	16	84	12	62	74

C. 15 Days After Resection-Vagotomy

Fasting	6	8	14	0	12	12
1 hour	32	12	44	0	26	26
2 hours	36	14	50	0	24	24
3 hours	30	12	42	0	32	32
4 hours	22	14	36	0	16	16

29 Days After Resection-Vagotomy

	Pouch			Stomach		
	Free	Combined	Total	Free	Combined	Total
Fasting	18	12	30	0	16	16
1 hour	52	10	62	0	52	52
2 hours	110	12	122	0	88	88
3 hours	118	10	128	0	40	40
4 hours	47	14	61	10	18	28
5 hours	20	12	32			

2 Mg. of Atropine, 32 Days After Resection-Vagotomy

Fasting	10	8	18	0	14	14
1 hour	16	12	28	0	10	10
2 hours	16	10	26	0	22	22
3 hours	20	10	30	0	30	30
4 hours	30	12	42	0	36	36
5 hours	72	16	88	10	56	66

42 Days After Resection-Vagotomy

Fasting	0	10	10	0	12	12
1 hour	80	10	90	0	28	28
2 hours	102	8	110	0	50	50
3 hours	98	8	106	0	36	36
4 hours	40	12	52	0	20	20

The formation of a Pavlov pouch had no appreciable effect on gastric secretion. Although from 25 to 30 per cent of the fundus was utilized for the construction of the pouch, after from two to three weeks the secretory response of the main stomach was practically the same as before the operation. The secretion from the pouch had a high acid titer.

After subtotal gastrectomy and double vagotomy a temporary diminution in acidity occurred in the secretions obtained from the main stomach remnant and the pouch in all of the animals, the acid values being approximately one-half the preoperative level. This phenomenon lasted approximately for from twelve to thirty-three days and represented a true depression in secretory activity because the acidity in the pouch was reduced approximately to the same extent as the acidity in the main stomach. It is important to note that the curves of total acidity in the pouch and main stomach tended to run a parallel course throughout the entire experiment and that one was practically always the counterpart of the other, the acid in the pouch being present nearly entirely as free hydrochloric acid and in the main stomach in the combined form. In the gastric remnant the acid values were usually lower than in the pouch, the difference depending probably on the degree of neutralization which resulted from the regurgitation of alkaline intestinal contents and the motility of the stomach.

Subsequently, the secretion of acid returned to its original preoperative level, the rate of recovery varying in different animals. In dogs 1, 2, 3, 4, 5 and 6 the acidity in the main stomach and pouch was found to have returned to its original values within from three to eight weeks after resection-vagotomy. Except for the fact that the maximum acidity in dogs 1 and 4 appeared from three to four hours after the test meal instead of in the second hour, the final curves of secretion could be very nearly superimposed on those obtained before operation (table 1 and charts 1 and 2). In dogs 7 and 8, after forty-two days and sixty days respectively, the acidity in the pouch was practically the same as before subtotal gastrectomy and vagotomy, but in the main stomach the total acidity remained somewhat lower than the original values (table 2 and charts 3 and 4). In dog 8, there was a secondary rise to maximum acidity in the fifth and sixth hours after the test meal in addition to the primary peak reached during the second and third hours. In these two animals the emptying time of the fundic remnant was extremely rapid and there was an unusual amount of regurgitation of intestinal contents, so that practically every sample contained large amounts of bile. The results of these experiments demonstrate that the total acidity in the main stomach after gastric resection depends on the motility of the fundic remnant, the

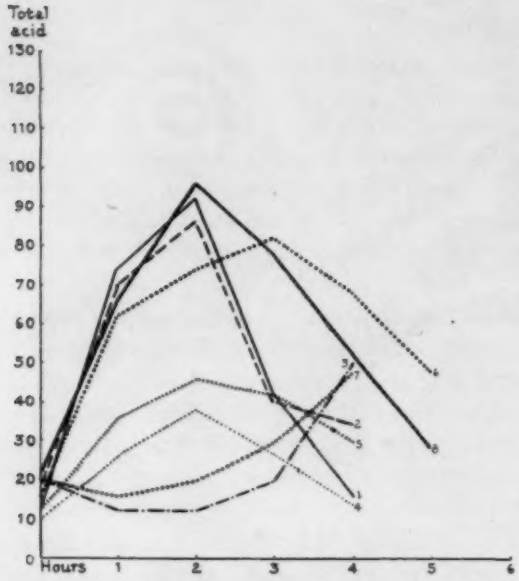

Chart 1 (dog 3).—Curves of total acidity in main stomach: *1*, before operation; *2*, after formation of Pavlov pouch; *3*, after formation of Pavlov pouch and injection of 2 mg. of atropine; *4*, twelve days after resection and vagotomy; *5*, twenty-six days after resection and vagotomy; *6*, thirty-three days after resection and vagotomy; *7*, thirty-five days after resection and vagotomy, with injection of 2 mg. of atropine; *8*, fifty-nine days after resection and vagotomy.

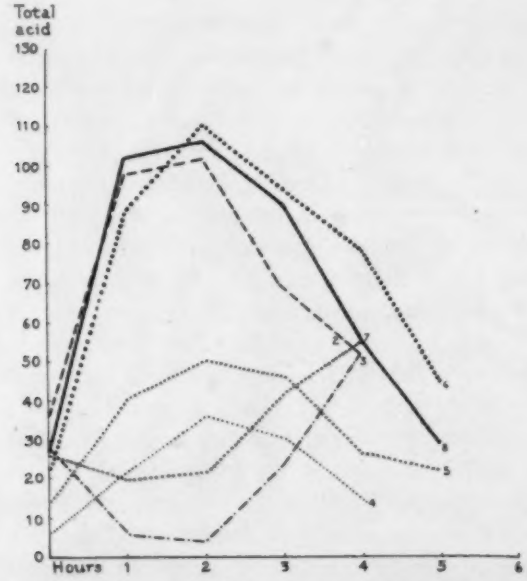

Chart 2 (dog 3).—Curves of total acidity in Pavlov pouch: *2*, after formation of Pavlov pouch; *3*, after formation of Pavlov pouch and injection of 2 mg. of atropine; *4*, twelve days after resection and vagotomy; *5*, twenty-six days after resection and vagotomy; *6*, thirty-three days after resection and vagotomy; *7*, thirty-five days after resection and vagotomy, with injection of 2 mg. of atropine; *8*, fifty-nine days after resection and vagotomy.

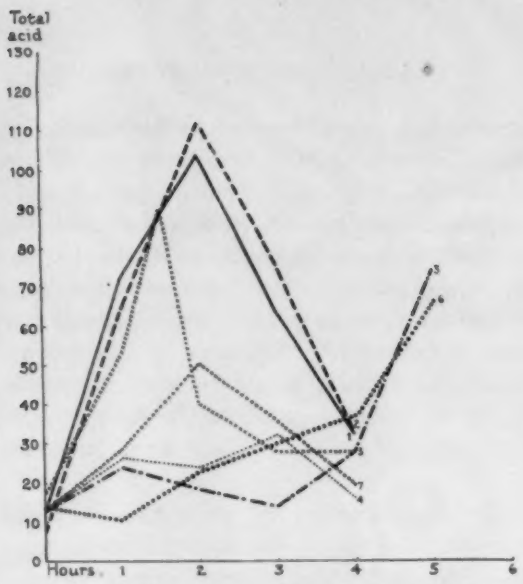

Chart 3 (dog 7).—Curves of total acidity in main stomach: *1*, before operation; *2*, after formation of Pavlov pouch; *3*, after formation of Pavlov pouch and injection of 2 mg. of atropine; *4*, fifteen days after resection and vagotomy; *5*, twenty-nine days after resection and vagotomy (bile, 4 plus); *6*, thirty-two days after resection and vagotomy, with injection of 2 mg. of atropine; *7*, forty-two days after resection and vagotomy (bile, 4 plus).

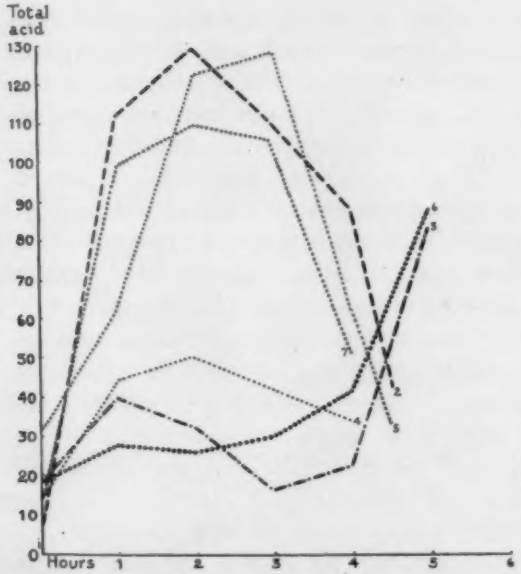

Chart 4 (dog 7).—Curves of total acidity in Pavlov pouch: *2*, after formation of Pavlov pouch; *3*, after formation of Pavlov pouch and injection of 2 mg. of atropine; *4*, fifteen days after resection and vagotomy; *5*, twenty-nine days after resection and vagotomy (bile in stomach, 4 plus); *6*, thirty-two days after resection and vagotomy, with injection of 2 mg. of atropine; *7*, forty-two days after resection and vagotomy (bile in stomach, 4 plus).

size of the stoma and the amount of neutralization by regurgitated intestinal fluids. The presence of secretory activity is shown by the good response of the pouch.

Atropine injected simultaneously with the administration of a test meal caused a marked depression in secretion in the pouch and main stomach in all of the animals. The inhibitory effect lasted from two to four hours and was just as marked after subtotal gastrectomy and double vagotomy as before. As the action of atropine wore off, secretion was resumed and the acid values gradually rose to a peak almost as high as the figures attained previously without atropine. Repeated injections prolonged the period of inhibition, but secretion always returned.

A rough parallelism between the curve of acidity and the rate of secretion occurred in the fundic remnant just as in the pouch. Since the magnitude of dilution of the gastric contents by the test meal was approximately the same before and after resection-vagotomy—the total volume of the test meal being alike under both conditions—changes in the rate of secretion were reflected roughly in the curve of acidity owing to the relatively constant dilution factor. Therefore, the return of acidity in the fundic remnant after resection-vagotomy was indirect evidence of the reestablishment of the secretory rate. This observation is particularly significant so far as the conditions in the fundic remnant are analogous to those which exist in man after subtotal gastrectomy.

Without trying to make any forced interpretation of the titration figures and curves presented, and fully aware of the variables and the limitations of the methods employed in this type of investigation, we believe that the sum total of three hundred acid titrations show definitely that sufficiently large amounts of acid occurred with a sufficient frequency to lead to the unavoidable conclusion that the physiologic mechanism of acid secretion was reestablished after resection-vagotomy.

During the progress of the experiments it was noted that the condition of the skin in the region of the Pavlov pouches was a good indicator of the amount of acid secreted at various stages of the investigation. As a rule, in dogs with Pavlov pouches, the skin adjacent to the external orifice is digested rapidly by the highly acid juice unless it is protected constantly by the application of neutralizing dressings, such as magnesium oxide powder and zinc oxide ointment. After gastric resection and vagotomy and concomitant with the temporary reduction in gastric acidity the neutralizing dressings could be dispensed with, and in cases in which digestion of the skin had occurred healing took place rapidly. However, after three or more weeks, with the gradual return of gastric acidity the skin began to break down again, and frequent neutralizing dressings had to be resumed in order to prevent extensive digestion of the abdominal wall.

At postmortem examination jejunal ulcers were found in two animals. In dog 3 there was a generalized peritonitis due to two perforated jejunal ulcers located about 8 cm. distal to the stoma. In addition, several smaller lesions were present. In dog 8 two marginal jejunal ulcers were found. One of them had perforated and the opening was sealed over by the tip of the quadrate lobe of the liver. Just distal to the suture line there was another superficial irregular jejunal ulcer. It is interesting to note that the gastric acidity in these animals was no higher than in the ones in which no ulcers developed. Others [33] have also reported the occurrence of jejunal ulcers in dogs after subtotal gastrectomy.

FACTORS CONCERNED IN THE RETURN OF GASTRIC ACIDITY AFTER SUBTOTAL GASTRECTOMY AND DOUBLE VAGOTOMY

The return of acidity after subtotal gastrectomy and double vagotomy is due to a number of factors which serve to maintain gastric secretion after the loss of the antrum and pylorus and division of the vagi.

First, section of the main branches of the vagi does not eliminate their influence on gastric secretory activity. This is demonstrated clearly by the studies with atropine which show that its pharmacologic action on the secretion of acid is practically the same after vagotomy as before. The vagi are parasympathetic nerves which terminate in the ganglionic plexuses of Meissner and Auerbach located in the wall of the stomach.[34] Kuntz [35] established the fact that these plexuses constitute an intrinsic reflex arc. Interruption of the continuity of the main vagus trunks cuts out the preganglionic fibers, but the postganglionic fibers remain intact. Atropine paralyzes the postganglionic mechanism of the parasympathetic nerves and arrests secretions which depend on central innervation. Its site of action is localized in the nerve endings or receptive substance and it is mutually antagonistic with pilocarpine.[36] This explains the phenomenon of atropine inhibition after section of the vagi. Since the entire intrinsic nervous mechanism of the stomach remains intact, it is evident that the phases of gastric secretion which are controlled by the vagi, namely the cephalic and

33. London.[18] Koennecke, W.: Experimentelle Untersuchungen über die Bedeutung des Pylorusmagens für die Ulcusgenese, Arch. f. klin. Chir. **120**:537, 1927. Ivy, A. C.: Personal communication to the authors.

34. McSwiney, B. A.: Innervation of the Stomach, Physiol. Rev. **11**:478, 1931.

35. Kuntz, A.: On the Occurrence of Reflex Arcs in the Myenteric and Submucous Plexuses, Anat. Rec. **24**:193, 1922.

36. Sollmann, T.: A Manual of Pharmacology, Philadelphia, W. B. Saunders Company, 1932, p. 389.

continuous phases, cannot be modified by vagotomy. Recently Klein [37] attempted to denervate transplanted gastric pouches by eliminating Auerbach's plexus, situated between the muscular layers of the wall of the stomach. However, it is practically impossible to denervate a pouch as long as the submucosa remains intact. Kuntz demonstrated that in the submucosa there are an enormous number of small ganglions and plexuses which send fibers to the muscularis mucosae, the glands in the mucosa and the gastric epithelium. The fibers which terminate in the epithelium are probably dendrites of neurons in the submucous plexus. The cells in the latter are probably of vagus origin, although some may be sympathetic. The histologic and pharmacologic studies of Ken Kuré and his co-workers [38] indicate that there are efferent parasympathetic fibers in some of the dorsal roots and other elements of the sympathetic nervous system which reach the stomach independent of the vagus. The splanchnic nerves, although predominantly inhibitory in nature, also carry excitatory fibers in them.[39] Obviously, division of the vagi does not affect these nerves.

Second, subtotal gastrectomy has only a temporary effect on the chemical phase of secretion. Although removal of the pylorus and antrum is accompanied by a reduction in acidity, the effect is a transient one and is followed by a return of acid secretion. Apparently, if a hormone is elaborated in this part of the stomach, its presence is not essential for the secretion of acid by the fundus. Local mechanical and chemical stimuli and secretagogues continue to act and contribute to the full recovery of the second phase.

Third, the intestinal phase remains unaltered and continues to exert an influence on secretion. The recent investigations of Crider and Thomas [40] indicate that reflex stimuli originating in the small intestine during digestion may be responsible for a larger proportion of the total gastric secretion than is manifest from previous studies. Moreover, after subtotal gastrectomy, the emptying time of the fundic remnant is shortened to one-half [19] and the influence of the intestinal phase manifests itself earlier than in the normal stomach.

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37. Klein, E.: Gastric Secretion: II. Studies in a Transplanted Gastric Pouch Without Auerbach's Plexus, Arch. Surg. **25**:442 (Sept.) 1932.

38. Kuré, Ken; Ichiko, Kin-Ichi, and Ishikawa, Kysusabura: On the Spinal Parasympathetic, Quart. J. Exper. Physiol. **21**:1, 1931. Kuré, Ken; Saegusa, Gen-Ichi; Kawaguchi, Ken, and Yamagata, Kenchi: On the Spinal Parasympathetic, ibid. **21**:103, 1931. Kuré, Ken; Ikeda, Ryoji; Ichika, Kin-Ichi, and Wada, Yasukiko: On the Spinal Parasympathetic, ibid. **21**:119, 1931.

39. Kuntz,[14b] p. 213.

40. Crider, J. O., and Thomas, J. E.: Influence of Certain Conditions in the Duodenum on the Rate of Secretion and Acidity of the Gastric Juices, Am. J. Physiol. **101**:25, 1932.

Fourth, the margin of reserve with respect to secretory surface area and the capacity of the glandular epithelium of the stomach to regenerate are factors which must be reckoned with in any attempt to diminish permanently by extensive gastric resection the amount of hydrochloric acid secreted by the fundus. Although exact quantitative studies have not been made, it is probable that the fundus, just like other secretory organs, such as the liver and pancreas, can accommodate itself to the extirpation of a large portion of its surface epithelium without any permanent diminution in the output of hydrochloric acid. The cytologic investigations of Griffini and Vassale [41] and of Ferguson [42] demonstrate the excellent regeneration of the gastric glands after the experimental removal of large areas of mucosa.

Finally, the results of tissue culture studies indicate that glandular epithelium, like other body tissues, tends to continue its functional activity when explanted. A pure strain of thyroid cells produces colloid morphologically identical with that found in the adult gland.[43] Kapel's [44] work indicates, on admittedly incomplete evidence, that embryonic gastric epithelium grown in vitro may secrete mucus and possibly enzymes. According to Kuntz, "secretion is an inherent function of gland cells, and constitutes a manifestation of their metabolic activity." Gastric secretion is not interrupted in the absence of nervous impulses, but continues subject only to the measure of control which is afforded by nonnervous factors.[45]

COMMENT

Although it is recognized that due allowances must be made for differences in species, we believe that the results of our experiments are significant with respect to man because the bulk of our knowledge concerning the physiology of the stomach is based on observations on dogs, which have been verified in man. In investigations dealing with estimations of gastric acidity, it is always necessary to distinguish between results due to neutralization factors and actual alterations in secretory activity. In dogs this can be done with relative ease by studying the pure secretions in pouches. In man it is more difficult

41. Griffini, L., and Vassale, G.: Ueber die Reproduktion der Magenschleimhaut, Beitr. z. path. Anat. u. z. allg. Path. **3**:428, 1888.

42. Ferguson, A. N.: A Cytological Study of the Regeneration of Gastric Glands Following the Experimental Removal of Large Areas of Mucosa, Am. J. Anat. **42**:403, 1928.

43. Ebeling, A. H.: A Pure Strain of Thyroid Cells and Its Characteristics, J. Exper. Med. **41**:337, 1925.

44. Kapel, O.: Einige Untersuchungen über das Verhalten des Epithels in Vitro, Arch. f. exper. Zellforsch. **8**:35, 1929.

45. Kuntz,[14b] p. 218.

to dissociate the two because indirect methods must be employed. Earlier in the paper it was pointed out that the reports in the literature concerning gastric secretion in man after subtotal removal of the stomach for ulcer were inconclusive, owing to inadequate methods. Since one of the primary objects of gastric resection is to induce a permanent reduction in acidity and since the results of experimental investigations indicate that intrinsic compensatory mechanisms militate against any permanent modifications in the secretion of hydrochloric acid, it is necessary to reinvestigate the problem, using more accurate methods than have been employed heretofore.

A sufficient length of time must be allowed to elapse before it can be determined definitely whether any permanent modification of gastric secretion has developed after subtotal gastrectomy. Gastric analyses should be made at frequent intervals and according to the fractional method for periods extending from four to six hours after the administration of a uniform test meal. The presence of bile in specimens of gastric contents is presumptive evidence that there is a large admixture of intestinal fluids, and under such conditions the acid values are unreliable owing to neutralization factors. With a small remnant of fundus and a large stoma it is important to ascertain the position of the tip of the aspirating tube by fluoroscopic examination in order to make sure that it is not too close to the lumen of the intestine. The emptying time of the stomach must be known. In the presence of a test meal the total acidity is a better gage of the output of hydrochloric acid than the free acidity, and the estimation of total chlorides may give additional corroboratory information concerning the secretion of acid. In the complete absence of titratable hydrochloric acid the potential secretory function of the gastric remnant can be determined by the response to histamine. The term "anacidity" is confusing because it is used by different investigators to convey different meanings and should be replaced by more definite terms, such as achlorhydria and hypochlorhydria. In interpreting the results of analyses the factor of individual variation and the limitations of the methods employed must be considered constantly. Attention to details of the type just outlined will render it possible to evaluate properly the end-results of subtotal resection for peptic ulcer in man with respect to gastric acidity.

CONCLUSIONS

1. Subtotal gastrectomy and double vagotomy in dogs induce only a temporary reduction in gastric acidity, which is due principally to a transient decrease in the secretory activity of the fundic remnant. This is followed by a return of acidity and secretory function.

2. The stomach is endowed with highly efficient compensatory mechanisms which provide for the continuation of secretion of hydrochloric acid by the fundus after removal of the antrum and pylorus and section of the vagi.

3. The fact that division of the vagi does not abolish the inhibitory action of atropine indicates that the intrinsic postganglionic mechanism remains intact.

4. Jejunal ulcers develop not infrequently after subtotal resection in dogs.

5. It is important to distinguish between a diminution in gastric acidity which is due to neutralization and a change which represents a real decrease in secretory function.

6. There is no experimental proof or convincing clinical evidence to support the hypothesis that subtotal gastrectomy, even combined with vagotomy, is the operation of choice for the surgical cure of peptic ulcer in man on the basis that it provides for a permanent lowering in the secretion of hydrochloric acid and thus prevents the development of recurrences and jejunal ulcers.

ABSORPTION OF UREA FROM THE BLADDER

FREDERICK A. FENDER, M.D.
BOSTON

For over one hundred years speculation has occurred in regard to the permeability of the bladder wall to physiologic as well as foreign substances. The reason for again taking up the subject is that a possible clinical application arose that seemed to warrant investigation. In a patient of this clinic, following an injury that amounted to transection of the cervical cord a marked cystitis developed, a complication that persisted in spite of cystotomy and generous lavage of the bladder. With this, there developed an abnormally high nonprotein nitrogen content of the blood, though a high fluid intake and output had been maintained, and though the function of the kidneys as measured by phenolsulphonphthalein excretion was good. In a conversation with Dr. Frank Fremont-Smith of the Harvard Neurological Unit, the possibility of reabsorption from the bladder was suggested as responsible for this turn of events, and the inquiry outlined here was undertaken in an effort to evaluate this possibility.

Though it has been done in earlier papers, some of the salient experiments may be capitulated. It should be made clear that the following material and the bibliographic references represent only fragments of the bulk of the work on this subject. For brevity's sake, only more prominent contributions have been included.

Kaupp,[1] as a medical student in 1856, compared specimens of his own urine voided hourly through the day with specimens retained for periods of twelve hours. Over a considerable period of time the retained urine was consistently lower in urea, water, sodium chloride, phosphates and sulphates. Kaupp believed this to be due to reabsorption of these into the blood stream.

Treskin,[2] in 1872, placed previously analyzed material into the bladders of dogs and reexamined specimens after the passage of various periods of time. Changes in the urea content, as well as in the volume, chlorides and specific gravity were thought attributable to interchange with the blood by diffusion through the bladder wall.

Ashdown [3] used three methods to establish his belief that the normal bladder is capable of absorption: He was able to poison dogs with

From the Neurosurgical Service of the Boston City Hospital, the Department of Surgery of Harvard Medical School and the Harvard Neurological Unit.

1. Kaupp, W.: Arch. f. physiol. Heilk. **15**:125, 1856.
2. Treskin: Arch. f. d. ges. Physiol. **5**:374, 1872.
3. Ashdown, H. H.: J. Anat. & Physiol. **21**:299, 1886-1887.

strychnine and other solutions introduced via a catheter; iodine identified by starch, was found to pass from the proximal ends of divided ureters after introduction into the bladder, a solution of urea decreased in concentration on remaining in the bladder.

Gerota,[4] in 1897, made observations on urine that had remained in the bladder after division and ligation of the ureters and found changes which he ascribed to absorption through a permeable bladder wall.

In the same year, Morro and Gabelein,[5] investigating the matter because of a possible clinical application, found that "mentionable" quantities of a number of substances introduced into the bladder of dogs were absorbed. Of salt, sugar, urea, boric acid, phenol, alcohol, potassium chloride, cocaine, quinine and morphine, only morphine failed of absorption. They concluded that great care should be taken in the clinical employment of cocaine (advice that has gone unheeded with fatal result since), and that phenol should not be used.

Cohnheim,[6] in 1901, closed the discussion for some years with a paper in which he reported work of a similar nature with a different outcome. He likewise, introduced "physiologic" and "nonphysiologic" or toxic material into the bladders of dogs, examining the first chemically before and after remaining in the bladder, and noting the systemic effects of the second. He concluded that the bladder wall is not a permeable membrane, even for water, unless a noxious substance has previously altered its native qualities.

Resuming investigation of the subject in this country, Macht,[7] in 1918, reported an interesting series of experiments on male dogs, taking as the criteria for his results systemic changes wrought by suitable substances placed in the bladder. Thus, the residual inhibitability of the heart by vagus stimulation was taken as evidence of atropine absorption, and fatal poisoning as indicative of absorption of nicotine. This investigator perhaps was the first to discriminate carefully between the respective rôles of the bladder and posterior urethra in absorption. He found little or no evidence of absorption of the three groups of substances studied, alkaloids (atropine, pilocarpine and nicotine), antiseptics (phenol and cresol) and anesthetics (cocaine and alypin), unless these were allowed to come into contact with the urethra. In this case, evidence of absorption usually appeared promptly. Even potassium cyanide, in doses of from 100 to 250 mg. failed of effect until it acted on the posterior urethra.

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4. Gerota, D.: Arch. f. Physiol., 1897, p. 428.
5. Morro and Gabelein: Ztschr. f. klin. Med. **32**:12, 1897.
6. Cohnheim, O.: Ztschr. f. Biol. **41**:331, 1901.
7. Macht, D. I.: J. Urol. **2**:43 (Feb.); 211 (June) 1918.

Two years later, Shoji,[8] using cats and rabbits, introduced physiologically-significant concentrations of salt solution. In addition to changes in the amounts of salt, the author noted absolute shifts in the water by observing changes in concentration of a substance (hemoglobin) in colloidal suspension. His results may be summarized thus: With 1 per cent solution, the water and salt remained the same; with 0.5 per cent, water was absorbed, and salt remained the same; with solutions of 0.25 per cent or less, there was a decrease in water and an increase in salt; in solutions of 2 per cent, the reverse of this took place. Shoji held it proved that the bladder epithelium is permeable to water and sodium chloride.

Mann and Magoun,[9] in 1923, assumed that absorption of small quantities of material can take place after recovering, from the proximal ends of divided ureters, phenolphthalein and indigo carmine previously introduced into the bladder.

The following year, Vickers and Marshal[10] found definite diminution in urea and salt left in the rabbit's bladder. A disproportionately great loss of urea with the use of 0.7 molar solution was thought due to injury of the bladder wall by the drug.

In 1925, Schönfeld and Müller[11] investigated absorption from the bladder in man from a clinical point of view, following deaths from the use of derivatives of cocaine. They found evidence of absorption of pilocarpine and tuberculin.

In spite of contradictions appearing in the foregoing, it seems reasonable, after analysis, to make several assumptions:

1. Excluding all part of the urethra, the bladder wall is slightly permeable to substances found normally in the urine, specifically, water, sodium chloride and urea.

2. Other substances may be transmitted to a slight extent, but the possibility of alterations in the normal physiology of the wall must be associated with any such consideration.

3. Trauma or inflammation grossly increases the permeability of the bladder.

These seem fair conclusions to draw. They do not embrace the whole question, but more specific conclusions involve considerable differences of opinion and cannot be said to rest on impregnable experimental work. The variations in results admit of several possible explanations that will not be discussed here, except to say that failure to

8. Shoji, R.: J. Physiol. **54**:239 (Dec.) 1920.

9. Mann, F. C., and Magoun, J. A. H.: A. J. M. Sc. **166**:96, 1923.

10. Vickers, J., and Marshal, E. D.: Am. J. Physiol. **70**:607, 1924.

11. Schönfeld, W., and Müller, W. G.: München. med. Wchnschr. **72**:291 (Feb. 20) 1925.

confine substances to the bladder alone and trauma inherent in the method must have affected the results in several cases.

The method that my co-workers and I used in our approach to the subject is a crude one, purposely so. Our interest was clinical, rather than physiologic, and designed to answer a specific question within certain limits. And the method, as shown by the negative control experiments, is suitable within those limits.

METHOD

Cats were anesthetized with sodium amytal, 7 cc. of a 1 per cent solution per kilogram of body weight being given intraperitoneally from twenty to thirty minutes before operation. At operation, a midline incision was made. The intestines were walled off with cotton moistened with warm physiologic solution of sodium chloride. The neck of the bladder was grasped in a fine snap. The ureters were tied and severed close to the bladder. Urine was withdrawn from, and substances introduced into, the bladder by means of a needle, the puncture being made in an avascular region, and the needle remaining in place throughout in order to avoid additional trauma. Specimens of blood were withdrawn from the vena cava from time to time with a fine needle, about 1.5 cc. being taken for each analysis. The cava was entered obliquely, and a warm, moist cotton pledget, laid gently against the puncture wound, sufficed to control hemorrhage. Care was taken to avoid irrelevant trauma, the bladder and other viscera being covered with cotton moistened with warm physiologic solution of sodium chloride during the extent of the experiment. The bladder was never distended to any extent by introduction of solutions, the amount introduced usually approximating that of urine withdrawn, and the injection being made very gently. Surgical solution of chlorinated soda (Dakin's solution) used was freshly made in each case. In the one instance in which it seemed that an active flow was not maintained in the vena cava, the whole experiment was discarded.

EXPERIMENTAL WORK

Specimens of blood from the vena cava were examined for non-protein nitrogen after the introduction of urea into the bladder, with and without previous irritation of the bladder mucosa by surgical solution of chlorinated soda. Two control experiments were carried out in which warm physiologic solution of sodium chloride was used in place of urea following irritation by the surgical solution. The pertinent experiments were those in which 10 per cent urea was placed in the bladder, and the experiment concerns these chiefly. One other experiment is reported to show that absorption readily takes place without previous irritation when a strong (50 per cent) solution is introduced. The specimens of heart blood were taken toward the end of each experiment to serve as a check on systemic absorption. Protocols of typical experiments follow:

Effect of Concentrated Urea.—Fifty per cent urea was introduced into the bladder without previous irritation of the mucosa. The animal used was a female cat weighing 3 Kg., which was anesthetized with 21 cc. of 1 per cent amytal.

Time	Comment	Blood nonprotein nitrogen, Mg. per 100 Cc.
:00	Operation carried out	
:05	Initial specimen of blood taken	57
:07	Urine withdrawn, 25 cc.	
:10	Urea introduced, 25 cc., 50 %	
:15	Blood specimen II (cava)	62
:45	Blood specimen III (cava)	80
1:15	Blood specimen IV (cava)	154
	Blood specimen V (heart)	100
1:45	Blood specimen VI (cava)	128
	Blood specimen VII (heart)	161

The bladder was incised at the conclusion of the experiment; it showed moderate injection. No hemorrhages were in evidence. A marked rise in blood nonprotein nitrogen was seen. This concentration of urea doubtless invalidates normal function of the bladder.

Experiment I.—Ten per cent urea was introduced into the bladder without previous irritation. The animal used was a male cat weighing 3.8 Kg., which was anesthetized with 26.5 cc. of 1 per cent amytal.

Time	Comment	Blood nonprotein nitrogen, Mg. per 100 Cc.
:00	Operation carried out	
:05	Initial specimen of blood taken	42
:09	Urine withdrawn, 15 cc.	
:10	Urea introduced, 25 cc., 10 % (slowly)	
:15	Blood specimen II (cava)	47
:45	Blood specimen III (cava)	45
1:15	Blood specimen IV (cava)	44
	Blood specimen V (heart)	43
1:45	Blood specimen VI (cava)	42
	Blood specimen VII (heart)	43

The incised bladder showed no apparent inflammation.

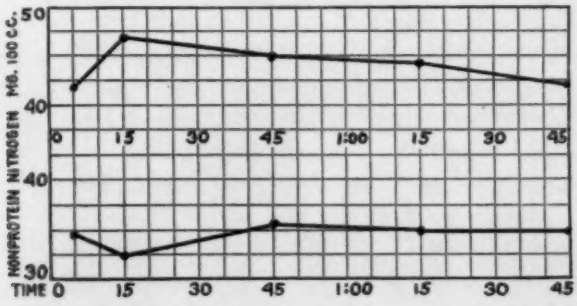

Chart 1.—Curves obtained in experiments I and II in which 10 per cent urea was introduced into the bladder without irritation of the mucosa.

EXPERIMENT II.—Ten per cent urea was introduced into the bladder without previous irritation (as in the foregoing experiments). The animal used was a male cat weighing 3.4 Kg., which was anesthetized with 24 cc. of 1 per cent amytal.

Time	Comment	Blood nonprotein nitrogen, Mg. per 100 Cc.
:00	Operation carried out	
:05	Initial specimen of blood taken	34
:07	Urine withdrawn, 49 cc.	
:10	Urea introduced, 35 cc., 10 %	
:15	Blood specimen II (cava)	33
:45	Blood specimen III (cava)	36
1:15	Blood specimen IV (cava)	35
	Blood specimen V (heart)	38
1:45	Blood specimen VI (cava)	35
	Blood specimen VII (heart)	39

The incised bladder showed no apparent inflammation.

The two foregoing experiments are taken to show that absorption of urea could not be detected by our method when the 10 per cent solution was introduced into the bladder without previous irritation.

EXPERIMENT III.—Ten per cent urea was introduced into the bladder following irritation for five minutes with surgical solution of chlorinated soda. The animal used was a female cat weighing 3.1 Kg., which was anesthetized with 22 cc. of 1 per cent amytal.

Time	Comment	Blood nonprotein nitrogen, Mg. per 100 Cc.
:00	Operation carried out	
:03	Initial specimen of blood taken	35
:09	Urine withdrawn, 75 cc.	
:10	Surgical solution of chlorinated soda introduced, 30 cc.	
:15	Surgical solution of chlorinated soda withdrawn	
:17	Urea introduced, 30 cc., 10 %	
:22	Blood specimen II (cava)	Lost
:52	Blood specimen III (cava)	59
1:22	Blood specimen IV (cava)	64
	Blood specimen V (heart)	55
1:52	Blood specimen VI (cava)	60
	Blood specimen VII (heart)	53

The incised bladder showed marked injection of the mucosa.

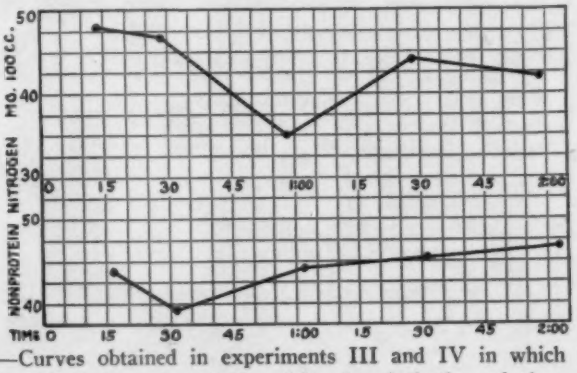

Chart 2.—Curves obtained in experiments III and IV in which 10 per cent urea was introduced into the bladder following irritation of the mucosa with surgical solution of chlorinated soda.

EXPERIMENT IV.—Ten per cent urea was introduced into the bladder following irritation for five minutes with surgical solution of chlorinated soda. The animal used was a male cat weighing 4.5 Kg., which was anesthetized with 30 cc. of 1 per cent amytal.

Time	Comment	Blood nonprotein nitrogen, Mg. per 100 Cc.
:00	Operation carried out	
:04	Initial specimen of blood taken	47
:10	Urine withdrawn, 23 cc.	
:11	Surgical solution of chlorinated soda introduced, 25 cc.	
:15	Surgical solution of chlorinated soda withdrawn	
:18	Urea introduced, 25 cc., 10 %	
:23	Blood specimen II (cava)	52
:53	Blood specimen III (cava)	84
1:23	Blood specimen IV (cava)	77
	Blood specimen V (heart)	74
1:53	Blood specimen VI (cava)	89
	Blood specimen VII (heart)	84

The incised bladder showed moderate injection of the mucosa.

The last two experiments, flanked by controls, are considered the significant experiments in this series. Two control experiments, in addition to I and II, were made as follows:

EXPERIMENT V.—The anesthetic, operative procedure and irritation by surgical solution of chlorinated soda were carried out as in the preceding experiments. Warm physiologic solution of sodium chloride was used instead of urea. The animal used was a male cat weighing 3 Kg., which was anesthetized with 21 cc. of 1 per cent amytal.

Time	Comment	Blood nonprotein nitrogen, Mg. per 100 Cc.
:00	Operation carried out	
:14	Initial specimen of blood taken	48
:15	Urine withdrawn, 10 cc.	
:16	Surgical solution of chlorinated soda introduced, 10 cc.	
:21	Surgical solution of chlorinated soda withdrawn	
:23	Saline introduced, 10 cc., warm	
:28	Blood specimen II (cava)	47
:58	Blood specimen III (cava)	35
1:28	Blood specimen IV (cava)	44
	Blood specimen V (heart)	48
1:58	Blood specimen VI (cava)	42
	Blood specimen VII (heart)	43

The incised bladder showed slightly reddened and inflamed mucosa. No hemorrhage was in evidence.

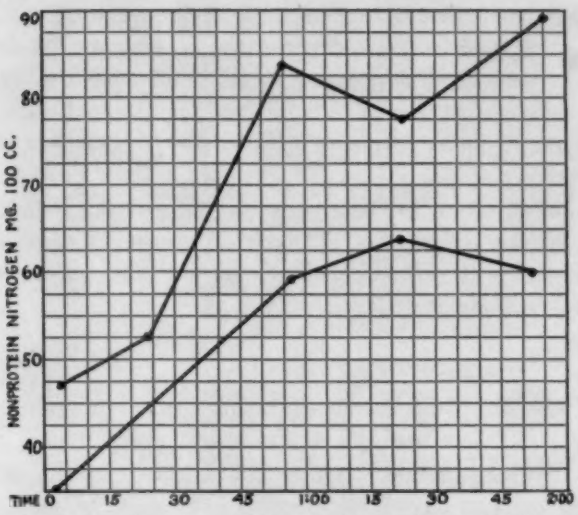

Chart 3.—Curves obtained in control experiments V and VI in which irritation was produced by surgical solution of chlorinated soda and physiologic solution of sodium chloride replaced the urea.

EXPERIMENT VI.—The procedure was the same as in experiment V. The animal used was a female cat weighing 4.2 Kg., which was anesthetized with 29 cc. of 1 per cent amytal.

Time	Comment	Blood nonprotein nitrogen, Mg. per 100 Cc.
:00	Operation carried out	
:17	Initial specimen of blood taken	44
:18	Urine withdrawn, 5 cc.	
:20	Surgical solution of chlorinated soda introduced, 15 cc.	
:25	Surgical solution of chlorinated soda withdrawn	
:26	Saline introduced, 15 cc.	
:31	Blood specimen II (cava)	39
1:01	Blood specimen III (cava)	44
1:31	Blood specimen IV (cava)	46
	Blood specimen V (heart)	52
2:01	Blood specimen VI (cava)	47
	Blood specimen VII (heart)	46

No inflammation of the incised bladder was evident.

COMMENT

It will be noticed that the second specimen of blood is taken five minutes after the significant maneuver in each case, and that the third, fourth and sixth follow at thirty minute intervals.

Additional experiments, patterned after the experiment reported, seemed, likewise, to show that this very strong solution of urea (50 per cent) so altered the bladder wall that absorption took place readily.

On the other hand, 10 per cent urea does not produce these changes to any such extent, and in this concentration the substance is not absorbed in quantities recognizable by our method. Following the inflammatory changes produced by surgical solution of chlorinated soda, however, there is a considerable rise (an average of 65 per cent in the two experiments).

The situation seems in some respects analogous to that encountered in the case of our patient, and we wonder whether absorption from an inflamed, imperfectly drained bladder may not have played an etiologic rôle in the development of his uremia.

CONCLUSIONS

1. The inflamed bladder mucosa transmits urea in quantities sufficient to raise the nonprotein nitrogen of the blood appreciably.

2. This mechanism may play an etiologic rôle in the development of uremia by patients having neurologically incapacitated bladders.

Dr. Tracy Putnam provided laboratory facilities and Miss Mary Dailey carried out the chemical analyses.

TREATMENT OF INFECTED WOUNDS OF THE BRAIN WITH BACTERIAL FILTRATES

J. R. B. BRANCH, M.D.

A. A. LEMPERT

AND

R. S. LYMAN, M.D.

SHANGHAI, CHINA

A number of soldiers were brought to the Chinese Red Cross General Hospital with wounds of the head sustained in the recent Sino-Japanese hostilities at Shanghai. All these wounds were infected. During the first few weeks of this period the outcome in each case seemed to be determined by the course of the infection. The wounds were treated in a routine manner by irrigation and dressings with surgical solution of chlorinated soda. During the last few weeks bacterial filtrates were used instead of the solution as a further means of controlling the infection. Eight of the last ten patients admitted with open infected wounds of the head involving the brain received treatment with filtrates. We herewith report the results of this treatment.

PROCEDURE

Smears and cultures were made from the wounds as soon as possible after the admission of the patients to the neurosurgical division. The surgical condition was then inspected, and the need of operation was decided on, with the help of a roentgenogram. If no operation seemed necessary, the use of surgical solution of chlorinated soda was discontinued and dressings soaked with polyvalent streptococcus-staphylococcus filtrate were applied. For the first day or so these dressings were changed several times; they were changed less frequently as time went on. If necessary, irrigation was carried out with a sterile physiologic solution of sodium chloride at the time when the dressings were being changed. In cases in which an operation seemed desirable, usually for the removal of fragments of bone or to provide adequate exposure of an infected area, surgical measures were carried out first; the wounds were dressed and drained with gauze moistened with bacterial filtrate; further applications of filtrate were made just as in the cases in which no operation was performed.

The bouillon filtrate was prepared for all cases in the following way: The respective strains of the organisms were allowed to incubate for two weeks and were then filtered through a Berkefeld filter. This was repeated by a second inoculation for the same period of time and a second filtration. A third inoculation of the filtered broth and incubation for seven days followed. All the strains were cultured separately in the course of the preparation of the bouillon filtrate. At the beginning of the work there were thirty-seven strains of staphylococci and

From the College of Medicine, National Central University, and the Medical Analysis Laboratories, Shanghai, China.

fourteen strains of streptococci, including Streptococcus viridans and Streptococcus haemolyticus. To this freshly prepared stock filtrate were added strains of streptococci obtained from the infected wounds of the patients under treatment.

RESULTS

CASE 1.—The patient sustained lacerations of the head when a bomb burst through the wall as he lay in bed. He remained unconscious for about two hours. A friend covered the bleeding wounds with dirty clothes. The next day the patient was taken to a hospital. He had a badly infected wound, which exposed the right parietal region of the brain through an opening 4 by 1.5 cm., and several infected lacerations of the scalp and face. For several days he was weak and unresponsive and had a high fever. There was an erythematous rash on the face. He was transferred to the Chinese Red Cross General Hospital on March 10. There was intermittent fever as high as 39.2 C. (102.7 F.) for about a week after admission. All the wounds were covered uniformly with a greenish-yellow exudate containing large numbers of gram-positive streptococci and diplococci. A culture taken on March 11 showed: Streptococcus haemolyticus, Streptococcus nonhaemolyticus (preponderance of growth), Staphylococcus aureus and Staphylococcus albus. The first treatment consisted of irrigation and dressings with surgical solution of chlorinated soda. There was no noticeable change in the appearance of the wounds, although as time went on the patient became responsive and cooperative and the fever disappeared. Bacterial filtrate was applied on the dressings used for the parietal wound as follows: On March 16 the filtrate was applied four times; at the end of the day the lower edge of the wound was pink; the rest was coated with purulent exudate. On March 17 the filtrate was applied three times; a band of pink granulation was seen at the lower part and along the upper edge of the wound. On March 18 the filtrate was applied once. Beginning on March 19, the filtrate was applied twice a day. The wound appeared clean except for a slender tongue of exudate. The parietal wound gradually became clean, and before the patient's discharge from the hospital it was completely covered by a growth from the surrounding scalp.

The smaller lacerations of the scalp were treated with irrigation and dressings with surgical solution of chlorinated soda until March 21. Although there was distinctly less purulent exudate from the wounds at the end of that time, they were still infected, and on March 21 treatment with the filtrate was applied for nine days, the dressings being changed only once a day. A burrowing gash on the right cheek failed to improve under dressings either of surgical solution of chlorinated soda or of filtrate, and on March 28 the wound was opened widely and was dressed with filtrate-soaked gauze. All the wounds of the head and face appeared clean by March 30 and proceeded to close in due time without further incident.

Summary.—A heavily infected parietal wound on the right side, which exposed the surface of the brain, showed little or no improvement under irrigation and dressings with surgical solution of chlorinated soda during two weeks of treatment. The first definite improvement appeared on the second day, and there was marked improvement on the fourth day, of treatment with filtrate. Improvement continued gradually until complete healing was effected. In the meantime small open lacerations of the scalp became clean under a combination of treatment with surgical solution of chlorinated soda and filtrate, but an infected burrow on the cheek resisted both types of therapy until it was widely opened surgically; it then healed promptly with the application of filtrate dressings.

CASE 2.—A tangential parieto-occipital wound on the left side was sustained early in February (the exact date is not known), which exposed the brain through an elliptic opening with a horizontal axis of 6 cm. and a vertical one of 3 cm. Initial unconsciousness, delirium and protracted delirioid behavior followed. Treatment was applied in the routine manner with irrigation and dressings with surgical solution of chlorinated soda, from the time of admission, on February 13, until March 11. In spite of this long period of treatment, the wound remained uniformly covered with a thick, dirty, grayish-yellow exudate. On March 9 a smear showed gram-positive and gram-negative diplococci and streptococci, gram-negative bacilli, polymorphonuclear cells and débris. A culture taken on the same date showed Staph. albus, Staph. citreus, and S. pyogenes, type 1. Dressings soaked in bacterial filtrate were then applied as follows: On March 11 a single application of filtrate was made late in the afternoon. On March 12 the filtrate was applied three times. On March 13 the filtrate was again applied three times; there was a slight subjective improvement. On March 14 the filtrate was applied twice; the upper part of the wound was free from exudate. On March 15 the filtrate was applied once, and, beginning on March 16, it was applied twice a day. On March 19 the exudate was limited to the lower edge of the wound and to a tongue that extended into the upper half. On March 22 the wound was almost entirely clean. A culture showed Bacillus cutis-communis and Bacillus pyocyaneus. A culture on March 24 showed Staph. albus, B. cutis-communis and B. pyocyaneus. The dressings with the bacterial filtrate were then discontinued, and dressings with surgical solution of chlorinated soda were resumed. In the course of a few days the wound began to be superficially clean for the first time, but evidence of a slight underlying residual infection remained, because the patient continued to have delirioid behavior. Soon afterward a transient phlebitis or lymphangitis of the neck developed. In spite of an apparently clean surface the wound failed to close during the rest of the patient's stay in the hospital. He was transferred elsewhere for further treatment.

Summary.—A badly infected tangential parieto-occipital wound on the left side, which exposed the surface of the brain, remained heavily coated with purulent exudate for a month under treatment with daily irrigation and dressings with surgical solution of chlorinated soda. On the third day of intensive treatment with filtrate there was a distinct improvement, which slowly continued until, on the eleventh day of therapy, the surface of the wound appeared clean. But the further course of the case indicated the existence of a residual underlying infection not completely cleared up while the patient remained in our care.

CASE 3.—On February 5 a tangential through-and-through bullet wound at the vertex of the skull drove fragments of bone into the underlying brain, for the most part just to the left side of the midline. Paralysis of all four extremities followed, but this condition improved rapidly. A purulent discharge from the wound decreased but did not disappear under treatment with irrigation with surgical solution of chlorinated soda. Paralysis of the right arm and leg and of the left foot remained stationary after the end of February. Surgical treatment was postponed until malaria was brought under control by quinine. An operation on March 30 evacuated a small amount of purulent material and led to the removal of four small fragments of bone embedded in the brain. A culture on March 16 showed Staph. aureus (abundant growth), a gram-positive streptobacillus and B. pseudodiphtheriae (a few). Dressings soaked with filtrate were then applied as follows: On April 1 the filtrate was applied four times. On April 2 the filtrate was applied three times; there was a slight immediate improvement in the motility

of the legs, but sensory changes were more extensive and severe than before the operation. On April 3 and 4 the filtrate was applied twice. On April 5 the filtrate dressings were discontinued. The wound appeared clean. Dressings with surgical solution of chlorinated soda were then instituted and were continued until the wound closed without incident. Sensory disorders decreased rapidly until the middle of April, when they and the motor paresis proceeded *pari passu* to a slow but definite improvement up to the time of the patient's transfer elsewhere.

Summary.—Small bony fragments were driven into the brain by a tangential through-and-through bullet wound at the extreme vertex of the skull. There was an initial clinical improvement as the purulent exudate from the wounds decreased with irrigation with surgical solution of chlorinated soda. The course was then stationary until operative exposure and removal of the embedded bony fragments. Postoperative dressings with bacterial filtrate were applied for four days, after which time the wound appeared clean; dressings treated with the solution of chlorinated soda were then applied, and healing continued to closure without incident.

Case 4.—The patient had received a penetrating wound in the right parietal region, caused by a bullet which was said to have been fired from a Japanese airplane. He had been admitted to a hospital elsewhere. The wound had closed promptly at the surface, but motor and sensory symptoms in the left arm and leg had increased. He was transferred to the Chinese Red Cross General Hospital on March 7. An operation performed on March 22 revealed an abscess of the brain, from which about 5 cc. of thick pus was evacuated. A culture of this material showed hemolytic and nonhemolytic streptococci. A cigaret drain soaked in bacterial filtrate was inserted, and the wound was closed around it. Dressings wet with filtrate were then applied as follows: On March 22 a cigaret drain and dressings soaked with filtrate were applied at the time of the operation. On March 23 the filtrate was applied three times. A drain moistened with filtrate was applied and was left in place. There was considerable pus. On March 24 the filtrate was applied twice; there was still considerable pus. From March 25 until April 5 the filtrate was applied once a day. On March 26 there was distinctly less pus on the dressings. By April 6 the purulent exudate had almost completely disappeared, and dressings with surgical solution of chlorinated soda were resumed. The first spontaneous movements of the left arm occurred on April 13. Improvement continued slowly, with complete closure of the wound, and the patient was eventually transferred elsewhere.

Summary.—A parietal bullet wound on the right side led to an abscess of the brain. After surgical exposure and drainage, the wound healed without incident under treatment with drains and dressings moistened with filtrate.

Case 5.—A through-and-through bullet wound sustained on February 21 left one opening in the right parietal region and another in the left occipital region. There was a slight purulent discharge from both wounds, intermittent fever for about a week and delirioid behavior for a few weeks after admission. Both wounds were enlarged to allow better drainage and were then treated with daily irrigation and dressings with surgical solution of chlorinated soda. In spite of this treatment the purulent discharge increased in amount from both wounds, particularly from that in the parietal region, where the patient complained of increasingly severe pain. A culture taken on March 9 showed Staph. citreus and Staph. epidermidis-albus. Both wounds were again given wider surface exposure on March 12, and dressings wet with filtrate were applied as follows to the parietal wound: On March 12 the filtrate was applied once, at the time of the operation.

On March 13 and 14 it was applied three times. From March 15 to March 21 it was applied twice a day. The patient suffered less pain. On March 16 there was an increase of purulent exudate. Beginning on March 21, the filtrate was applied once a day. On March 23 the patient experienced dizziness, choked disks, slight ataxia on the left side and paresis of the left arm. On March 24 an operation revealed a deep abscess in the right parietal region, from which 3 to 4 cc. of thick pus was obtained and four or five fragments of loose bone were removed. A culture taken on March 24 showed nonhemolytic streptococci, Staph. epidermidis-albus and B. pyocyaneus. A cigaret drain was inserted, wet with filtrate, and the wound was covered with gauze moistened with the filtrate. After the operation the parietal wound was treated daily with filtrate dressings as before. For a while the weakness and incoordination on the left side were worse than before, but pain decreased, and the choked disks promptly improved. The wound soon became clean and healed slowly without further incident.

Until the first of April the surface of the occipital wound had appeared relatively clean and was treated with daily dressings with surgical solution of chlorinated soda. But beginning on April 1 an increasing amount of purulent discharge came from it each day. On April 14 a wide incision was made in the occipital part of the scalp; about 15 cc. of pus was evacuated from the scalp and about 2 cc. was evacuated from a small underlying abscess of the brain. Bacterial filtrate was then applied for the first time by means of the dressings used for the occipital wound, according to the following schedule: On April 14 the filtrate was applied four times; on April 15 it was applied three times; beginning on April 16, it was applied twice a day. On April 16 herniation of the brain began to develop through the occipital bony opening. For the next ten days, the condition remained unchanged. The herniating mass was surrounded by pus which exuded from under the edges of the bone. Dressings with surgical solution of chlorinated soda were resumed in place of those with the filtrate. On April 27 the herniating mass was cut away and the base of the wound was sealed by the use of high frequency current. Another herniating mass developed, but the wound remained cleaner on the surface than before. On May 21 the mass was treated with 156 mg.-hrs. of radium; the hernia receded at once, leaving a clean granulating wound by the end of May.

Summary.—A through-and-through bullet wound became infected at the points of entrance and exit, in the right parietal and left occipital regions. Superficial exposure of the wounds, followed by irrigations and dressings with surgical solution of chlorinated soda, failed to cure the infection within three weeks. Further superficial exposure and treatment of the parietal wound with filtrate for eleven days failed to bring improvement. An operation revealed a deep abscess of the brain in the right parietal region. After evacuation of the abscess and drainage and dressings with the filtrate, the wound proceeded to heal without further incident. Then purulent exudate increased in the occipital wound. An operation evacuated considerable pus from the scalp and revealed a small abscess of the brain. A hernia of the brain immediately appeared, with pus exuding in small amounts from under the bone. Neither treatment with filtrate nor irrigation with surgical solution of chlorinated soda brought immediate improvement. Three weeks after the appearance of the hernia the occipital wound also appeared clean and the hernia receded.

Case 6.—A wound of the left frontal region, exposing the brain, had become infected. Removal of fragments of bone, drainage and irrigation and dressings with surgical solution of chlorinated soda and with saline solution had been

carried out elsewhere. The patient was transferred to the Chinese Red Cross General Hospital on March 18, with an infected, bloody mass protruding slightly through the opening in the frontal bone. A smear showed gram-positive streptococci, diplococci and some staphylococci. Cultures taken on March 18 and 19 showed Str. haemolyticus, Staph. albus and Sarcina subflava. The patient was stuporous, febrile and toxic; there were harsh bronchovesicular breath sounds and tachypnea. Dressings soaked with filtrate were applied as follows: On March 18 the filtrate was applied once, in the evening. On March 19 the filtrate was applied three times. A lumbar puncture revealed 2,650 cells; reducing substances, 29.4, and chlorides, 676. The spinal fluid gave a positive reaction for globulin; the Wassermann reaction was negative. A culture showed no growth. On March 20 and 21 filtrate was applied twice a day, and, beginning on March 22, it was applied once a day. Soon after admission the patient grew profoundly stuporous and definite signs of meningitis developed. Repeated lumbar punctures yielded results similar to the first. A positive culture of Str. haemolyticus was later obtained from the spinal fluid, but a blood culture showed no growth. The patient died on March 28.

Summary.—An infected frontal wound on the left side, exposing the brain, showed no improvement following the application of filtrate in a patient with toxemia from a disseminated infection. Death occurred eight days after admission.

Case 7.—A tangential wound at the extreme vertex of the skull drove fragments of bone into the brain. The patient had had first aid treatment and dressings before he was transferred to the Chinese Red Cross General Hospital on March 16. On admission he was quiet, and the wound allowed good contact, but a large infected fungating mass protruded from the opening in the skull. Cultures taken on March 18 and 19 showed Staph. aureus and Micrococcus gingivalis; a few colonies of nonhemolytic streptococci were recovered on the following day. The initial dressings with surgical solution of chlorinated soda were changed for surface dressings with filtrate, but after a few days it was obvious that the filtrate did not reach the underlying seat of the infection. On March 23 the herniating mass was destroyed by fulguration and filtrate dressings were continued. Another mass with its attendant purulent coating pushed out through the bony opening. Dressings with the filtrate were discontinued after a few more days, and irrigation and dressings with surgical solution of chlorinated soda were instituted. Various measures, surgical and physiologic, were applied through dehydration, but the fungating mass continued to develop. The patient grew stuporous and died on April 8. Autopsy showed bony fragments embedded deep in the upper left parietal region and a wide zone containing inflammatory and hemorrhagic plaques in the upper half of both hemispheres, particularly on the left side and around the left lateral ventricle.

Summary.—A tangential wound at the vertex of the skull drove fragments of bone into the brain. The patient was transferred to the Chinese Red Cross General Hospital with an infected hernia of the brain. There was no improvement under superficial treatment with filtrate. The patient became stuporous and died. Autopsy showed widespread inflammation in the brain around the wound and in the left lateral ventricle.

Case 8.—The patient sustained a through-and-through bullet wound from the left temporal to the left frontal region, just above the orbit of the eye, on April 8. At operation, on April 12, an apparently clean field was opened, with considerable attendant bleeding. The track of the bullet was exposed; in only one place, the size of a pea, was the meningeal covering of the frontal pole torn through by

the bullet. A few bony fragments outside the meninges were removed. A culture taken from the field at the time of operation showed no growth. Treatment by packing with gauze to control bleeding and by applying dressings soaked with filtrate was instituted. Postoperative dressings with filtrate were applied four times on April 13, three times on April 14 and twice a day from April 15 to May 3. On April 16 there was a seropurulent discharge from the frontal wound. On April 19 sanguinopurulent material gushed from the temporal wound when the packing was removed. On April 21 there was a thick purulent discharge from both wounds and frontal irrigation came from the nose. At this time a culture showed a heavy growth of Str. haemolyticus and Staph. aureus. On May 3 a second operation was performed; the field was reexposed and better drainage was provided. The wound closed without further incident under treatment with daily dressings with surgical solution of chlorinated soda.

Summary.—Four days after a through-and-through bullet wound extending from the left temporal to the left frontal region was sustained, an operation exposed the track of the bullet. Treatment with prophylactic drains and dressings soaked in filtrate was followed by the appearance of a heavy infection, which did not clear up until a second operation gave still wider exposure and treatment with dressings with surgical solution of chlorinated soda was instituted.

COMMENT

The cases reported here are too few to warrant a final decision as to the value of bacterial filtrates in the treatment of infected wounds of the brain. Yet from these few observations some points stand out as leads for further investigation.

In the first place, the frequent application of bacterial filtrates to fully exposed wounds of the brain or to meninges with surface infection may prove to be very effective. In the series presented, only the first two cases fall in this category. The improvement in the appearance of the wounds, which were both infected predominantly with hemolytic streptococci, was striking after treatment with filtrates began to be intensively applied. Emphasis is laid on three points which appear to be requisite for success with this type of treatment: 1. Exposure must be complete so that the whole infected surface is brought in contact with the dressings. 2. The dressings should be moistened with the filtrate at frequent intervals. 3. The infection must be focal and limited to the surface of the wound. The first case reported gives an illustration of the necessity of observing these points. The parietal wound which exposed the brain was heavily infected but was wide open, and the infection was superficial. This was the first wound to become clean under treatment with filtrates. The superficial lacerations of the scalp, to which filtrates were applied later and less often, cleared up next. But the burrowing gash on the face resisted applications of both surgical solution of chlorinated soda and filtrate until it was opened widely with the knife and dressed with gauze soaked in filtrate. In the second case there was a widely exposed wound in which the infec-

tion seemed to be limited to the surface. With intensive use of filtrates the change in the appearance of the wound was quite as definite as in the first case, for the superficial infection cleared up rapidly under this treatment, but the final result was not so good, a fact which is attributed to the likelihood of a slight but persistent infectious process in the underlying tissues.

A second feature in this series of observations is the length of time before results became apparent. In several of these cases treatment with bouillon filtrate was continued for from one to three weeks. In only two cases can any success be claimed with this treatment (cases 1 and 2). In both these cases treatment with prolonged irrigation and dressings with surgical solution of chlorinated soda led to little or no change, but within four days after intensive use of filtrates was begun a pronounced improvement took place. The suggestion is accordingly made that bacterial filtrates are indicated in all cases of open wounds exposing the meninges or brain which appear superficially infected with streptococci or staphylococci, and that improvement in the appearance of the wound will be definite within four days, if at all. If no improvement has taken place after four days of intensive trial of the treatment with filtrates one must consider the likelihood of an extension of the infection beyond the surface of the wound, e. g., focal or diffuse encephalitis, abscess of the brain, ventriculitis, meningitis or a pus pocket under the scalp. As examples, in case 5 of this report there were abscesses of the brain; in case 6, encephalitis and meningitis, and in case 7, encephalitis and ventriculitis.

In two cases in this series (3 and 4), a recognized abscess or focal encephalitis developed at the site of the wound before treatment with filtrates was considered. The areas were opened at operation, and drains, packing and dressings were applied as usual, except that they were moistened with filtrate instead of with surgical solution of chlorinated soda or some other bactericidal solution. Also, with the parietal abscess in case 5, postoperative dressings were wet with filtrate. In all three cases the healing of the wounds took place satisfactorily. No statement can be made from these cases alone, however, as to the relative merits of using filtrates or other applications on drains or dressings after operation for the abscesses of the brain. For in regard to effectiveness and to the rate of closure of infected wounds lying deeper in the brain tissue we could see no difference between the results obtained with surgical solution of chlorinated soda and those obtained with Bezredka's filtrates on the postoperative dressings. But we are inclined to lay aside, at least for the time being, the use of bacterial filtrates in the treatment of abscesses of the brain. We see no special advantage in their use in such cases, and there are distinct theoretical difficulties in establishing contact between the whole infected

area and the drains, as well as in maintaining sufficient concentration of the filtrate to be effective inside the abscesses.

Finally, the action of the filtrates could be that of a bacteriophage. The therapy was successful only on production of conditions which were favorable to that action: infection with the streptococcus and staphylococcus already present, polyvalent streptococcus-staphylococcus filtrate, an open wound to provide good contact and frequent moistening of the dressings to give the necessary concentration of filtrate. The other objective which was suggested during the work with the filtrates was the establishing of local immunity in the tissues surrounding the infection. But so far we have no clinical proof that such an action is possible in the brain and meninges, and there is some evidence against it. The patient in case 8 came to us soon after his injury. The track of the bullet appeared to be clean at the time of the first operation, and a culture showed no growth. But the application of bacterial filtrate for the sake of providing local immunity as a prophylactic measure against infection was soon followed by a severe infection with Str. haemolyticus and Staph. aureus. Furthermore, unpublished experiments performed on rabbits, while not conclusive, gave no positive indication that local immunity can be developed in brain tissue by saturating it with Bezredka's streptococcus filtrates.

Thus the clinical results obtained by us in treating infected wounds of the brain with bacterial filtrates, the proposed indications for its use and the theory of bacteriophage action all fall in line. Theoretically this therapy should work with rapidity when the proper filtrate is brought in good contact with bacterial growth in sufficient concentration to cause lysis of the organisms; practically the results seem to become apparent within about four days or less in cases with surface infection of thoroughly exposed wounds when the dressings are repeatedly moistened with the proper filtrate. Failure to obtain improvement within four days may be taken as an indication of improper contact or of insufficient concentration, that is, of a poorly matched filtrate, inadequate exposure of the wound, a deep or disseminated infection or some other clinical complication.

SUMMARY

1. Two patients with severely infected wounds on the surface of the brain showed marked improvement within four days following frequent applications of a polyvalent streptococcus-staphylococcus filtrate to the dressings. Prior to treatment with the filtrate they had shown no improvement with irrigation and dressings with surgical solution of chlorinated soda.

2. Three patients with infected wounds of the brain showed no improvement after more than four days' trial of treatment with filtrates. These patients later proved to have a deep or disseminated infection of the central nervous system.

3. It is suggested that the successful results were due to bacteriophage action, which requires good contact of the filtrate in sufficient concentration to cause lysis of the bacterial organisms. The treatment indicated is frequent moistening of the dressings with the proper filtrate. The clinical indications for this treatment are a wide exposure of the wound and a surface infection of the brain or meninges. Improvement should begin within four days if this type of treatment is to be adequate.

A REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.
LOS ANGELES

E. STARR JUDD, M.D.
ROCHESTER, MINN.

LINWOOD D. KEYSER, M.D.
ROANOKE, VA.

JEAN VERBRUGGE, M.D.
ANTWERP, BELGIUM

ADOLPH A. KUTZMANN, M.D.
LOS ANGELES

ALEXANDER B. HEPLER, M.D.
SEATTLE

AND

ROBERT GUTIERREZ, M.D.
NEW YORK

(Concluded from page 1166, December, 1933)

URETER

Transplantation.—Ormond [28] reported that the rectum and lower part of the sigmoid flexure are the customary sites for ureteral transplants, and although the content of these segments constitutes a definite objection, and renal infections do occur, the functional results are reasonably good. Occasionally technical obstacles to the use of the sigmoid flexure or rectum are encountered, making it necessary to use a higher part of the bowel, and in a number of such instances the right ureter has been implanted into the cecum.

A series of experiments on animals was carried out. The procedure in all cases was the same: first, implantation of the right ureter into the cecum, following Coffey's technic as nearly as possible; second, about ten days later, removal of the left kidney. The animals all recovered rapidly from the first operation, and after the first day were as active as before. At first, after the second operation, there seemed to be no change, but gradually they became less active, and finally went into a semistuporous condition. At death, the value for nonprotein nitrogen of the blood was much elevated.

Ormond's interpretation of these findings, taken in conjunction with other experimental work, is that urine, emptying into the cecum,

28. Ormond, J. K.: Some Experimental Work on the Site for Ureteral Transplant, J. Urol. **29**:15 (Jan.) 1933.

is reabsorbed, at least in great part, and entering the blood stream is again passed through the kidneys, again excreted and reabsorbed, and so on. Consequently, the products that normally are removed by the kidneys accumulate in the blood until uremia and death occur. Moreover, the kidneys themselves are injured by the strain thrown on them by perfusion with blood that is overlooked with urinary constituents. His conclusion is that transplantation of the right ureter into the cecum is at best a useless procedure, and may be harmful, as is suggested by the occasional presence of injury to the mucosa at the point of entrance of the ureter.

Quénu and Fey [29] stated that on two occasions they had cut a ureter accidentally, following which they performed ureterocystoneostomy; in both cases repair was made immediately, and the patients were cured without a fistula. The second case, controlled urologically two years later, presented certain points of considerable interest. In this case, the ureterocystoneostomy was performed only a few moments after the ureter had been cut, during an operation for removal of a large fibroma. The paramount consideration here was the conservation of a sound kidney with normal secretion. Every ureterocystoneostomy which does not achieve this end should be regarded as a failure. For the success of such an operation it must be determined that the kidney conserved functions normally. Neither clinical nor cystoscopic proof alone is sufficient to show that this object has been attained, for clinical healing may coincide with the death of a kidney. A number of experiments, operative findings and postmortem examinations have shown that a ureter may contract and even become obliterated, and a kidney may undergo dilatation and atrophy, without any symptoms. For this reason, 30 or more cases reported in the literature are useless scientifically, since they bring no other proof of cure. Only 1 of the 50 cases reported can meet the criterion of functional examination after bilateral catheterization, which makes it possible to judge of renal function by the quantity and quality of the urine secreted in a given time. This may be due in part to the site of the neostomy, the surgeon having, for his own convenience, made an implantation into the dome of the bladder too high to permit catheterization.

Although the authors' case has not yet stood the test of time, they regard the result obtained as astonishingly good, because, first, the patient feels well; second, the orifice of the neostomy, permeable to the catheter, is neither obliterated nor contracted; third, vesicorenal reflux is prevented; fourth, neither the ureter nor the pelvis is dilated; fifth, the

29. Quénu, Jean, and Fey, Bernard: Résultat éloigné d'une urétéro-cystonéostomié, Bull. et mém. Soc. nat. de chir. **58**:1377 (Nov. 16) 1932.

urine collected in the pelvis is uninfected, and sixth, the kidney secretes a normal quantity of urine containing urea and sodium chloride in a concentration greater than on the opposite side. In addition to the usual functional tests, they also have examined the patient cytobiologically and cystographically, and by intravenous pyelography. Absence of reflux, of reno-ureteral dilatation and of infection suggests a good prognosis.

Without being fully able to account for their good result, the authors ventured to state that the following procedures may have played a part: first, the immediate implantation of a freshly cut ureter in a case in which the kidney was neither dilated nor infected; second, selection of the site of implantation as near as possible to the normal ureteral orifice; third, the use of the Payne procedure of implantation, with two sutures at a distance from the orifice, and fourth, decision not to introduce a catheter either during or after operation.

[COMPILERS' NOTE.—The problem of reimplantation of the ureter into the bladder after any surgical injury during operation has attracted considerable attention for many years, but in reality the value of this procedure has never been actually tested until cystography and, more properly, intravenous urography came into use, by which the condition of the kidney could be tested functionally. It has been the general belief that the kidney ultimately was destroyed by the vesicoureterorenal reflux which, in turn, was caused by lack of sphincteric action at the newly formed ureteral orifice; also, by the tension of the ureter which distorted the bladder and interfered with the dynamic contractions of the ureter and the emptying time of the renal pelvis. However, Quénu and Fey apparently have satisfied the requirements, although sufficient time has not as yet elapsed to prove the final outcome, for not infrequently urinary infection, pyelonephritis, hydroureter and hydronephrosis ultimately develop, and these may eventually call for ureteronephrectomy.]

Beer,[30] in a recent communication read before the New York Academy of Medicine, reviewed his results in a group of 41 cases in which ureterocystoneostomy had been performed, as determined by intravenous urography, although in many of the cases cystography revealed the presence of vesicorenal reflux, and in some of them catheterization of the ureters has never been possible. It can be concluded, therefore, that although ureterocystoneostomy should be performed in an attempt to save the kidney whenever the ureter has been injured, the patient should be informed of the possibilities of a surgical lesion developing at a future time.

30. Beer, Edwin: Value of Ureteral Re-Implantation in the Bladder, Am. J. Surg. **20**:8 (April) 1933.

Obstruction.—Ockerblad [31] reported 27 cases of noncalculous, acute ureteral obstruction. The oldest patient was 68 years of age and the youngest, 2 years. Fourteen patients were females and 13 were males. In all of them, pain was the predominant symptom, varying slightly in degree. In each case there was an elevation of temperature, ranging from 100 to 105 F. In 19 there was a chill. In 22 of the cases nausea or vomiting, or both, occurred. In 4 cases the urine in the kidney was bloody when withdrawn by catheter. In every case the urine was under pressure. The amount withdrawn varied from 20 to 500 cc. Invariably some pus was present in the urine from the obstructed kidney. In every case relief from pain was immediate on ureteral catheterization.

The various etiologic factors presented an interesting study. In 11 cases the cause of obstruction was unknown. Of the remaining 16 cases, 1 was definitely an instance of the wandering kidney described by Dietl. In 1 case a congenitally solitary kidney was blocked by seminal vesiculitis. One patient was a pregnant woman, in the fifth month of gestation. In another case, that of an infant, the condition was the result of congenital stricture of the ureter. In 1 case both ureters were tied at operation. In 1 case an appendical abscess was present; an aberrant blood vessel to the lower pole interfered with the ureter in 1 case; in 2 cases there were tuberculous strictures of the ureter; operative scars closed the intramural portion of the ureter in 2 cases; in 3 cases strictures closed the ureteral os, and large prostatic lobes growing upward under the mucosa impinged on the ureter in 2 cases. It is interesting that there were 5 congenital anomalies. There were no deaths from the disease. The two outstanding points in the diagnosis are the pain and the finding of urine under pressure.

Woytek [32] stated that "pseudonephrolithiasis" is the term applied by Allemann to that condition in which the symptoms are caused by organic inflammatory kinks and strictures in the upper part of the ureter, causing disturbances in function. These cases simulate closely cases of true stone, since colic and microscopic hematuria are often present. The cause is usually an inflammatory process of the perirenal tissue or of the kidney itself. Movable kidneys are associated with only a small number of cases. Woytek has seen 60 such cases since 1924 and has divided them into 2 groups: first, the cases with sudden onset, and second, those with gradual onset. Cases of the first group simulate cases of colic caused by stone; nearly always microscopic examination reveals blood in the urine along with the colic.

The author expressed the belief that some physicians do not accurately study their cases and consequently report large numbers in

31. Ockerblad, N. F.: Acute Ureteral Obstruction, J. Urol. **29**:32 (Jan.) 1933.

32. Woytek, G.: Ueber "Pseudonephrolithiasis," Beitr. z. klin. Chir. **156**:389, 1932.

which ureteral strictures were found. On the other hand, at the Mayo Clinic, where the cases are well studied, only 6 cases in which definite strictures were encountered were found in the course of 6,000 cystoscopic examinations. In further studies made elsewhere (Braasch, Kenneth Frater) 2 cases of stricture were found in 93 cases. Schreiber found stricture in 13 per cent, whereas Campbell, in 13,000 postmortem examinations, observed stricture in only 1 per cent.

Woytek suggested that infection carried from foci by the blood stream often causes ureteral stricture (tonsillitis, influenza, scarlet fever, diphtheria, puerperal sepsis, otitis media, infections of teeth, enteritis, salpingitis, prostatitis and seminal vesiculitis). The characteristic findings seem to be infiltration of the mucosa and musculature with round cells.

Absolute proof of ureteral stricture or kink is best given by retrograde ureteropyelograms. Intravenous urography can be of secondary help.

Treatment is chiefly conservative. In cases in which there is irreparable injury to the ureters it may be necessary to perform nephrectomy.

Granuloma.—Hamer, Mertz and Wishard [33] stated that granulomas of the ureter do not give rise to pathognomonic symptoms. Hematuria, usually recurrent and gross, is the chief complaint. The passage of large clots may cause colicky pain. Positive physical findings depend on the presence of obstruction and on loss of blood and infection; they are not pathognomonic. They stated that the gross appearance of a ureteral granuloma varies according to the extent of the lesion. There may be thickening of the ureteral wall, with increased vascularity and evidence of a periureteral inflammatory reaction. In the event of an extensive local lesion, a distinct tumor may be palpated in the ureter. On section, the ureteral mucosa is found paved with reddish-purplish granulation tissue which bleeds easily when traumatized. If there is sufficient proliferation, polypoid masses may be present. There may be single or multiple areas, which may become confluent and may involve a considerable extent of ureter.

The authors expressed the belief that the most significant special urologic finding is in the pyelo-ureterogram, and indeed one cannot allow anything pathognomonic in its interpretation. The point of error lies in suspecting a true neoplasm. Obviously, the urographic findings must be protean, depending not only on the extent of surface involved, but also on the degree of proliferation and consequent type of filling defect observed. Single or multiple circumscribed filling defects,

33. Hamer, H. G.; Mertz, H. O., and Wishard, W. N., Jr.: Ureteral Granuloma, J. Urol. **29**:43 (Jan.) 1933.

together with a possible ragged appearance of the ureteral edges, may suggest neoplasm, granuloma or possibly tuberculosis.

Hamer, Mertz and Wishard suggested that without any means of establishing a definite diagnosis, treatment is obviously going to tend toward open operation, unfortunate as this may be in the presence of granuloma. When one has reasonable doubt as to the presence of a neoplasm, one may resort to ureteral dilation and medication directed toward the clearing up of both local infection and distant foci, but one dare not persist too long, unless improvement appears, lest the opportune time for removal of a true neoplasm be lost. On the other hand, hemorrhage may be so severe as to endanger the patient's life unless immediate operation is done. In conclusion, the authors stated that in view of the possibility of bilateral involvement, nephro-ureterectomy is warranted only in an emergency.

Nerve Supply.—Wharton [34] stated that the ureter receives a nerve supply which is independent of the innervation of the kidney and bladder. The nerves go directly to the ureter from the lowest renal ganglion, at the upper end of the spermatic plexus and from the abominal sympathetic nerves. Their dissection disclosed that there is a connection between the ureteral innervation and the plexuses that supply the ovary, testis and parietal peritoneum.

Wharton said that from the physiologic point of view, his clinical observations would lead him to conclude that cutting these ureteral nerves, as in ureteral denervation, does not interfere with the motor function of the ureter and does not cause atony, hydro-ureter, stricture or any ureteral disturbance. On the basis of clinical observations, he is of the opinion that one of the functions of these ureteral nerves is the transmission of painful sensations.

PROSTATE GLAND

Prostatectomy.—Illyes [35] used a tampon for hemostasis in suprapubic prostatectomy. After the arterial bleeding has been controlled, the assistant inserts a finger into the rectum to hold up the prostatic cavity, following which the tampon is packed carefully and evenly throughout the entire cavity. The tampon is left in for five days, during which the cavity is washed out alternately with ice cold water and with very warm water if bleeding occurs. Illyes has had practically no bleeding following this technic and is well satisfied with it.

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34. Wharton, L. R.: The Innervation of the Ureter, with Respect to Denervation, J. Urol. **28**:639 (Dec.) 1932.

35. Illyes, G. V.: Ueber die Tamponade nach Prostatektomie, Ztschr. f. urol. Chir. **36**:183, 1933.

[COMPILERS' NOTE.—Packing of the prostatic cavity with gauze has been employed extensively at various times in this country. Many surgeons still do this, claiming good results, and prefer it to the use of various types of hemostatic bags. The Hagner and Pilcher bags, and other modifications, are used in place of gauze in most clinics at the present time. They are simpler to use and efficient, cause little pain, and can be removed without causing secondary bleeding. Little is now written in this country concerning tampons and bags, for the descriptions of the newer operation of prostatic excision has practically displaced articles on prostatectomy.]

Transurethral Resection.—Bumpus [36] has reviewed 102 cases of urinary obstruction due to benign enlargement of the prostate gland in which he performed the transurethral operation, from 1925 to 1927. He chose this period for two reasons: first, because it gave a period of five years since the last operation, and second, because he had operated in more than 100 cases in the preceding years and felt that any failure that might be disclosed would not be ascribed to inexperience but to the procedure. In half of these cases Bumpus used the Câulk cautery punch, and in the other half, a modification of Braasch's cystoscope. The amount of residual urine prior to operation in the 102 cases varied from none to a large quantity resulting from complete retention; in 22 cases, the quantity was in excess of 200 cc. Fifty-seven patients were free from residual urine at the time of dismissal, and 15 others had less than 30 cc., making a total of 72 whose immediate postoperative result indicated success for the future.

After a survey of the 102 cases, five or more years after operation, Bumpus reported that 8 of the patients were dead. During the five years following operation in this series, transurethral resection was performed in approximately 300 cases, and 4 deaths occurred; none of these deaths was directly or indirectly attributable to bleeding, but was the result of infection following failure to remove sufficient tissue and completely eliminate residual urine. More than 100 patients had been operated on successfully since the last death. Records to date were available of 66 of the 102 patients. Adenofibromatous tissue was removed from 24 of them, of whom 18, or three fourths, had written that they were satisfied with the final results. Of 6 dissatisfied patients, 3 underwent prostatectomy, one a year later, another two years later and a third four years later.

Bumpus stated that records are available to date on 42 of 67 cases in which transurethral resection was done for inflammatory changes

36. Bumpus, H. C., Jr.: Results Five Years After Transurethral Treatment of Benign Prostatic Obstruction, J. Urol. **28**:564 (Nov.) 1932.

in the prostate gland. Thirty of the patients have expressed satisfaction with the final results, whereas 12 are definitely disappointed.

Bumpus stated that this study of 102 cases in which prostatic tissue was removed through the urethra more than five years before, because of urinary obstruction, would indicate that with the improvement in technic which has occurred in the last five years, transurethral resection should be performed with less risk, with less time spent in the hospital and consequently with less expenditure of funds, and that the final functional result would equal in permanence that usually obtained after prostatectomy.

In a study of 250 cases in which transurethral resection was done in the last seven years, Bumpus [37] found that in 204 cases (81.6 per cent) 5 Gm. of tissue or less was removed. If it is estimated that two fifths of the hypertrophic tissue removed at prostatectomy represents the amount that is actually obstructing the urethra, one may consider any prostate gland the hypertrophic portion of which weighs less than 50 Gm. as suitable for transurethral resection. In but 32 per cent of 575 cases in which prostatectomy was performed at the Mayo Clinic in the last three years did the removed tissue weigh more than 50 Gm. But included in this 32 per cent are many cases in which the patients had complete retention, extensive renal impairment and often grave cardiac injury, not to mention extreme senility in some cases, when they were first seen. Such patients require suprapubic drainage at the earliest moment consistent with safety, and, needless to add, relief of the obstruction should be undertaken with the minimum of risk. The institution of suprapubic drainage greatly extends the applicability of transurethral resection for reasons already stated. As a result, at the clinic it was found possible to relieve patients of their suprapubic drains in cases in which the risks had seemed too great to warrant prostatectomy.

Up to January, 1932, Bumpus had removed the obstructing portion of the prostate gland in 44 cases in which cystostomy had been performed previously. In 19 of these, the cystostomy had been done as the first stage of prostatectomy in two stages, but the decrease in the size of the gland after drainage, or more frequently the poor physical condition of the patient, made the transurethral method of removal seem preferable.

Among the 44 patients were 3 with carcinoma of the prostate gland who previously had undergone suprapubic drainage and, becoming dissatisfied with the arrangement, demanded relief. One of these patients, aged 73, died of embolic pneumonia. In the remaining 72 cases in which cystostomy had been performed, the transurethral method of treatment

37. Bumpus, H. C., Jr.: Prostatic Obstruction Relieved by Suprapubic Drainage Followed by Transurethral Resection, Tr. Am. A. Genito-Urin. Surgeons **25**: 211, 1932.

was used because the urinary obstruction was not great. In 12 of these 22 cases, recent resection of a diverticulum made another major operation a thing to be avoided, and in the remaining 10, removal of stones from the bladder had resulted in so much diminution in the size of the prostate gland that prostatectomy hardly seemed justified for removal of so comparatively small an amount of tissue. Letters were received from 38 of the patients who accepted transurethral resection after previous cystostomy. Twenty-nine expressed themselves as satisfied with the results, whereas 9 were disappointed.

Bumpus concluded that although transurethral removal of obstructing prostatic tissue had been made possible by electrocoagulation, the applicability of transurethral resection has been extended by the performance of suprapubic cystostomy prior to resection. Suprapubic cystostomy is especially useful in operating on patients who are suffering some serious impairment of parenchymatous organs.

Crowell and Davis [38] attempted to analyze clinically, by questionnaire and by personal examination, results in 385 cases in which transurethral resection had been carried out according to their plan in the last five years. Two hundred ninety-nine patients returned the answered questionnaire, and 49 reported for examination. One hundred and seven patients had not returned definite replies to the questionnaire.

The authors found that the clinical results obtained were better in cases in which operation had been performed more than six months before the questionnaire was answered. There is nearly always some tenderness, accompanied by tenesmus, during and following urination for several months after the operation, but this finally subsides. They presumed that with time the remaining portion of the gland becomes atrophied and retracts so as to enlarge the vesical opening and enable the patient to empty the bladder without difficulty. A number of the patients were subjected to cystoscopy from one to five years after operation, and the prostatic urethra was found unobstructed by the remaining portion of the gland.

In the analysis of questionnaires and reexaminations, it appeared that 247 patients had no difficulty in emptying the bladder, while 16 did have difficulty. Of these patients, 110 emptied the bladder once at night; 77, two or three times, and 59 not at all. Three had incontinence, and 5 noted leakage at times when the bladder was full. Ninety-three had gained weight, and 133 had not changed in weight.

Day [39] considered an initial series of 71 cases in which loop resection was performed by seven different urologists. Fifty-three oper-

38. Crowell, A. J., and Davis, T. M.: Results in 385 Cases of Prostatic Resection by the Davis Method, Tr. Am. A. Genito-Urin. Surgeons **25**:215, 1932.

39. Day, Robert: Endoscopic Resection of the Prostate, J. Urol. **28**:569 (Nov.) 1932.

ations were performed on clinical patients, all in the same hospital, and 18 were on private patients. Eleven resections were performed by the same attending urologist in his clinical service; 21 were about evenly divided among five other urologists in the service, and the remainder were performed by Day himself. There were 9 deaths, 6 from primary hemorrhage and ensuing shock, 2 from multiple abscesses of the kidney and 1 from acute dilatation of the heart. The mortality rate for the entire series was 12.7 per cent. The first 41 patients of the series were unselected. In size, most of the prostate glands were graded 4. All of the deaths were among these first 41 patients, a mortality rate of 22 per cent. A considerable percentage of these 41 patients had been considered either completely unfit for prostatectomy or as extremely bad risks. The remaining 30 were selected, 18 of whom were private patients; none of these 30 patients died. The most frequent cause of death was primary hemorrhage with ensuing shock. In the later series of selected cases the freedom from undue bleeding was attributed, for the most part, to the employment of a two-machine hook-up. Day stated that in his total personal series of 39 cases in which major loop resection was performed, there were 2 deaths. Four of the 71 patients in the series were later subjected to prostatectomy.

Malignancy.—Smith [40] summarized the effect of radium applied to the prostate gland in 31 operations on 29 patients. There were 6 deaths from operation, 3 of which were due to pulmonary emboli. Nine other patients died of carcinoma within one year. The average length of life of those patients who survived operation but who died of carcinoma was thirteen and a half months. Seven of the patients were still alive when the report was written, 4 patients less than one year, 1 thirteen months, 1 eighteen months and 1 four years after operation.

Smith said that in 3 cases it was demonstrated that carcinomatous cells had survived extensive irradiation (from 3,800 to 5,000 millicurie hours). Since it is not feasible to destroy the entire prostate gland by massive, destructive radiation, the object of treatment by radium should be to employ a dose insufficient to cause extensive necrosis, with a view to causing fibrosis and a decrease in the malignancy of the tumor.

Brandesky [41] found 154 cases of sarcoma of the prostate gland in a review of the literature, and added a case of his own. Sarcoma of the prostate gland is rare, usually afflicting young subjects. In the reported cases, 31 per cent of the patients were in the first decade of life; 17 per cent had passed the age of 50. The prognosis is always unfavorable.

40. Smith, G. G.: What Does Radium Do to the Malignant Prostate? Tr. Am. A. Genito-Urin. Surgeons **25**:155, 1932.

41. Brandesky, Walter: Primäre Prostatasarkome, Wien. med. Wchnschr. **82**:182, 1932; abstr., Am. J. Cancer **16**:1183, 1932.

Brandesky's patient was a man, aged 56 years, who had urinary obstruction. Cystotomy was done, following which the patient had repeated attacks of burning pain and tenesmus. Rectal palpation revealed a large, soft, fluctuating prostate gland protruding into the rectum. Three months after cystotomy the tumor was partially removed. It was adherent to the rectum and grossly was of papillary structure. Microscopic examination revealed a necrotic, spindle cell sarcoma. The patient died shortly afterward, and at necropsy the diagnosis of sarcoma of the prostate gland was confirmed.

BLADDER

Tumors.—Müller [42] reported on conditions of the urinary bladder in workers in aniline dyes at Basel. There were 4 cases of acute hemorrhagic cystitis, 1 case of chronic ulcerative cystitis, 19 papillomas of which 6 later became malignant and 36 definite carcinomas. The time in which the worker had been handling different chemicals varied from two to thirty-six years, averaging seventeen years and four months. For the 9 benign tumors, the average was fourteen years, and for carcinoma, nineteen years.

In contrast to the observation of Simon, who found a fairly low degree of malignancy in aniline carcinomas, the growths at Basel were highly malignant and rarely operable, and readily formed metastatic growths. The papillomas in Müller's cases were treated satisfactorily by endovesical fulguration. In 5 cases of carcinoma in which the tumor was in a satisfactory area resection of the bladder was done. Of these patients, 2 were well and working eight years after operation. In cases in which the tumor was on the side wall and base of the bladder, cystectomy was done, the ureters being transplanted into the intestine.

A rigid system of examination and prophylaxis is being carried out among the chemical workers in Basel. The urine is examined at regular intervals, and any patients who have suggestive symptoms are examined cystoscopically.

Redi and Marri [43] stated that the indications for extensive operation in cases of malignant tumor of the bladder are drawn chiefly from the size of the tumor, its base of implantation, its extent in surface and depth, the presence of metastasis and the general condition of the patient. Although total cystectomy is the operation of choice when the growth is extensive, in most cases the situation of the tumor and its infiltration into the wall of the bladder indicate partial cystectomy; this

42. Müller, Achilles: Ueber Blasenveränderungen durch Amine, Ztschr. f. urol. Chir. **36**:202 (Jan.) 1933.

43. Redi, Rodolfo and Marri, Piero: Sulla resezione parziale della vescica urinaria per cancro infiltrate e sulla consecutiva rigenerazione della parete vescicale, Arch. ital. di urol. **10**:3 (Jan.) 1933.

can be done even when the entire wall of the bladder, except the trigone with the ureteral orifices, is involved. The resection may be followed by suture, or suture may not be employed; even in the latter case, the bladder regenerates completely. A case in which Redi operated is of particular interest from the surgical standpoint, in that partial resection of the bladder was accomplished suprapubically by use of the electric knife. The tumor, which was composed of highly typical cells, involved the entire left half of the bladder; it was limited posteriorly by the ureteral orifice and anteriorly by the median line of the organ. When it was seen that the ureteral orifice was not invaded by the tumor, Redi preserved it, although he extensively coagulated this area. The entire left half of the bladder was removed, and the remainder of the cavity was packed around a permanent catheter. Two weeks later, where the left half of the bladder had been, a smooth, shiny, pinkish wall had been developed, differing markedly from the mucosa. By the end of a month there was a well defined left vesicular cavity, rather more extensive than the right half. There was no ureteral reflux, and the general condition of the patient was excellent. When the report was written, one year had passed since the operation, and there had been no sign of recurrence.

Marri, who made the pathologic examination of the specimen, found complete absence of epithelial pearls or of any tendency to cornification, which showed that the growth was highly malignant. Absence of cornification is one of the characteristics of those forms which ulcerate readily, spreading through the walls of the bladder and extending to adjacent structures. That the tumor was of definitely infiltrative type, however, is shown by the fact that the vesical wall itself was irregularly invaded in every direction by the epithelial extensions; the invasion stopped just short of the peripheral portions of the wall. Examination of tissue from the newly formed vesical wall, on the sixtieth day following operation, revealed regeneration that included all the walls, thus proving that for such a result it is not necessary to make use of a suture for the purpose of reconstructing a vesical cavity. In some tracts the epithelium was completely reconstituted; in some places it was identical with normal epithelium, and in the other areas nearly so. The elements were roundish, thick-set and rather large, evidently following a biologic law common to the various tissues in these cases, but not to be confused with pathologic processes of proliferation with which it had no relation. Amitotic division was observed everywhere, but never mitosis. The histologic observations led to the conclusion that this regeneration had come from the margins of the urinary bladder remaining after resection of the diseased portion. The regeneration applied to all strata of the wall, muscular and mucosal.

Godard and Koliopoulos,[44] although they expressed belief in the usual methods of treatment of carcinoma of the bladder of women, advised cystectomy in cases in which ordinary methods are impracticable. Cystectomy is logical only when combined with total hysterectomy; a bloc formed of the bladder, uterus, related lymphatic regions and vesicovaginal zone corresponding to the trigone should be removed in one piece.

An operation in two stages is done. The first stage is bilateral cutaneous iliac ureterostomy by Papin's method. This preliminary step has also the advantage of permitting exploration of the condition of the kidneys and ureters, which will reveal whether cystectomy is feasible. Preoperative care consists of lavage of the bladder, administration of vaccine and, when there has been profuse hematuria, transfusion.

Cystectomy is indicated for malignant tumors of the floor of the bladder, tumors of the trigone and most tumors of the lateral surface of the bladder. Partial cystectomy is nearly always insufficient, but may be done for early carcinoma of the dome of the bladder. One should be certain that the carcinoma is not secondary.

The final operation is performed in stages: First, the adnexa are removed, and the utero-ovarian and round ligaments are tied. Second, the umbilico-uterine arterial trunk is isolated and tied, and the uterosacral ligament is sectioned. This second stage is accomplished by dissection of the umbilical artery, freeing of the origin of the uterine artery, and tying of the common trunk above the latter. In exceptional cases the hypogastric artery must also be tied. As soon as section of the uterosacral ligament is accomplished, the uterus becomes movable and rises easily. Third, the neck of the bladder is liberated and sectioned. Fourth, the vagina is sectioned. Fifth, peritonization is performed, followed by the placing of a vaginal drain. A suture is drawn from right to left, uniting the prevesical peritoneum to the sigmoid part of the colon.

The survival of patients, as reported by various authors in cases in which cystectomy has been performed, is as follows: five years and four years (Heresco), eight years (Nicholitch), five years (Wolff), from one to six years in 6 cases (Albarran), from two to six years (Werhogen) and sixteen years (Pawlick). Watson, in 16 of 62 cases had cures lasting "several years." Simon reported 2 cases in which the ureters were implanted into the intestine, with 1 death from postoperative uremia and 1 death three months later. Beer reported that five years after total cystectomy he had observed recurrence of the malignant growth in the iliac region.

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44. Godard, Henri, and Koliopoulos, A.: La cystectomie totale chez la femme dans le cancer de la vessie, Rev. de chir., Paris **70**:201 (March) 1932.

Cystectomy, despite its gravity, is indicated for epitheliomas and sarcomas that resist physical agents; exceptionally, also, in the course of a Wertheim operation for carcinoma of the uterine cervix, when one encounters invasion of the floor of the bladder and has to operate in a single stage.

Chwalla [45] concluded, from his experience with vesical carcinomas, that with the exception of those carcinomas which involve the base and neck of the bladder, it is best to resect all, since cure is thus more likely. Although Chwalla's operative results are not unusual, he has achieved a large number of apparent cures; 40 per cent of the patients have had no recurrence eight years after operation. In cases of carcinoma of the base of the bladder, Chwalla stated that he treats only symptomatically or not at all. If the carcinoma is obstructive, a suprapubic fistula is made. He expressed the belief that cystectomy, as judged by the results reported, is hardly justified at present. He also gives as his opinion that the best results and improvement in the future will rest on early diagnosis and early operation. An early diagnosis is possible; every patient with hematuria should undergo cystoscopy, and every patient with urinary disturbance should be examined urologically.

Barringer [46] stated that from 30 to 55 per cent of carcinomas of the bladder can be controlled by proper irradiation for three years or more. He reported 129 cases. In 98 cases, the clinical diagnosis was supported by biopsy. In this group, 52.9 per cent of 51 patients with papillary carcinomas and 29.7 per cent of patients with infiltrating carcinomas of the bladder were alive without evidence of disease at the end of three years.

Barringer advocated suprapubic cystotomy and implantation of radon seeds in the treatment of carcinoma of the bladder. He used gold seeds of radon, containing from 1 to 1.5 millicuries. He implanted a gold seed in each square centimeter of the base of the tumor. His operative mortality was only 4 per cent in 109 consecutive cases. He expressed the belief that it is possible to control from 10 to 15 per cent of carcinomas of the prostate gland for three years or more by irradiation. If the disease is confined to the posterior region of the prostate gland, between the fascial planes, without involvement of the vesical neck, the use of radon needles, implanted through the perineum, is advised. In cases in which the tumor involves the neck of the bladder, cystotomy and implantation of gold seeds of radon into the prostatic tumor are preferable.

45. Chwalla, Rudolf: Das Carcinom der Harnblase und der gegenwärtige Stand seiner Behandlung, Ztschr. f. urol. Chir. **35**:251, 1932.

46. Barringer, B. S.: Bladder and Prostatic Carcinoma, J. M. Soc. New Jersey **29**:115 (Feb.) 1932.

Sauer [47] reported a case of endometriosis of the urinary bladder. The patient was a woman, aged 40, who had severe dysuria and hematuria for nine months. Cystoscopy revealed a mass, the size of a cherry, on the posterior wall of the bladder in the median line. It protruded into the bladder and was surrounded by a region of bullous edema. There was no definite inflammation in the bladder or around the tumor. The patient was operated on, and the tumor was removed with wide resection. It was thought at the time of operation, judging from the consistency and appearance of the tumor, that it unquestionably was malignant. Microscopic examination revealed typical endometriosis.

Diverticulum.—Spinelli [48] stated that although most diverticula of the bladder are acquired, a small number are evidently congenital, for they are found in fetuses and associated with other malformations. They increase in frequency with the age of the patients, reaching their maximal frequency in the fifth or sixth decade of life. They are rare among women, and it is significant that they develop in the same decades as obstructions of the bladder and urethra from various causes.

In order of importance, the site of diverticula is: first, the lateral walls of the bladder; second, the floor of the bladder; third, the ureteral and periureteral regions, and fourth, the dome and posterior wall. This distribution is based on anatomic findings of points of lessened resistance to continued increase of pressure, which yield and permit cellules and diverticula to form.

When the normal habitual force necessary to empty the bladder has become increased by conditions which obstruct the normal outflow of urine, the mechanism of production of diverticula becomes evident. Lesions which cause obstruction to the outflow would act pathologically as follows: first, through insufficient emptying of the bladder, resulting in urinary stasis; second, through the effort of the detrusor to overcome the obstruction; third, through the distention and atony which injure the detrusor in cases of incomplete chronic obstruction; fourth, through the tendency of the stagnant urine to become infected, and fifth, through incoordinated and violent contractions to which the bladder is subjected after cystitis has developed. Under any of the conditions named, the muscle attempts vigorously to overcome the obstacle. This is followed by hypertrophy of the musculature and a characteristic appearance of the bladder in columns, with marked weakness of the walls, especially at the points of congenital inferiority. It is just at these points that the mucosa of the bladder tends to open between the trabeculae of the columns or between the openings of the meshes, while

47. Sauer, H.: Ueber einen Fall von Endometriose der Harnblase, Zentralbl. f. Gynäk. **57**:347 (Feb. 11) 1933.

48. Spinelli, Antonino: I. Diverticoli della vescica, Policlinico (sez. chir.) **39**: 390 (June 15) 1932.

the process of inflammation which always accompanies these lesions, infiltrating the muscular wall, renders it less elastic and more liable to give way. Thus the diverticulum begins, and as the pressure increases, it gains in size. The wall is soon infiltrated by the inflammatory process, which produces abundant connective tissue of a poor sort, almost always devoid of elastic and muscular fibers, while on the outside the inflammatory process extends by contiguity to the nearby parts and forms cicatricial bridles which also impair the elasticity of the same wall.

The diverticulum becomes evident only when complications arise. The functional symptoms most frequently met are dysuria, retention, interrupted micturition and terminal pyuria; on these the diagnosis is based. Left to itself, the diverticulum grows larger, and may give rise to four types of complications: mechanical, infective and inflammatory, calculous and neoplastic, and ascending disturbances. Spinelli uses the suprapubic route as the most convenient approach to a diverticulum of the bladder. The postoperative course after removal is generally good. The mortality rate, according to various authors, is 9.91, 10 and 13 per cent; functional insufficiency remains in about 20 per cent of the cases.

Rupture.—Mark [49] observed the innocuousness of mediums for intravenous urography, and suggested their use in the diagnosis of ruptured bladder. He stated that 35 cc. of 40 per cent skiodan was given intravenously while the patient was on a Bucky diaphragm. Seven minutes following the start of the injection, the first roentgenogram was taken and eight minutes after the injection was started, the second was taken. These roentgenograms disclosed extraperitoneal rupture into the space of Retzius, with most marked extravasation on the left. The patient was immediately taken into the operating room, the diagnosis substantiated and repair instituted.

Mark stated that use of this method in cases of suspected rupture of the kidney of lesser degree and in cases of suspected rupture of the bladder is simple and innocuous, and should apply to both intraperitoneal and extraperitoneal rupture. It appears to be free from the objectionable features that might be held against the usual methods of diagnosis.

Hernia.—Oberlin [50] found, in the literature, reports of only 13 cases of perineal hernia of the bladder, to which he added the report of a case of his own. Of the entire 14 patients, 10 were females. There are two types of perineal hernia, median and lateral. The median type, due to abnormal depth of Douglas' culdesac, pressing either on the wall of the

49. Mark, E. G.: Intravenous Urography in the Diagnosis of Rupture of the Bladder, J. A. M. A. **100**:42 (Jan. 7) 1933.

50. Oberlin, Serge: Hernie périnéale de la vessie, Bull. et mém. Soc. nat. de chir. **58**:1237 (Oct. 19) 1932.

rectum or on that of the vagina, comprises both hydroceles and elytroceles. Lateral hernias, on the contrary, emerge through the fibers of the levator ani or insinuate themselves between this muscle and the ischiococcygeal muscle. The position of the hernia with reference to the transverse perineal muscle is difficult to establish, since it is hardly visible, owing to the pushing back or distortion of this muscle by the development of the hernia. Anterolateral perineal hernia had been reported only in the male; it is caused by trauma and does not, properly speaking, constitute a true hernia. Apart from these, all perineal hernias of the bladder are posterior; however they may begin, they end by passing behind the urogenital diaphragm and taking a position between the anus and the ischium.

In Oberlin's case, the hernia, coming from the small pelvis, passed obliquely backward, crossing the axis of the vagina. A series of roentgenoscopic and roentgenographic views indicated that the content of the sac was not intestine or omentum. Because the swelling was easily reducible, the diagnosis of cold abscess was excluded; a diagnosis of hernia of the bladder was made. This hernia was constituted by a prolongation of the bladder that communicated widely with the rest of the organ, and in no sense formed a diverticulum. It was accompanied by a sort of funnel that replaced the trigone. The bladder was of normal capacity, but was much deformed in contour; it was flattened transversely, with the two lateral walls almost vertical and very close together. On the sides of the funnel the two ureteral orifices could be seen, in normal condition. There was no interureteral muscle; the funnel stretched out behind the orifices, which seemed nearer to the neck of the bladder than is usual. The levator muscle was represented by only a few fibers, stretched out and atrophied, on the surface of the hernia. A sound introduced through the urethra and bent downward and to the left easily penetrated the herniated portion of the bladder and could be felt on palpation.

To push the pocket back into position was simple. It was much more difficult to reconstruct the floor of the perineum, in view of the poor quality of the tissues available for use. Oberlin could make a reconstruction only in a single layer, taking in the gluteus maximums and a few remnants of the levator ani and fixing them within the wall of the vagina. Thus, an insecure curtain was drawn under the bladder, and the skin was sutured over a horsehair drain. The results were excellent for two years, after which the hernia recurred. It was a remarkable fact that the patient had never suffered the least inconvenience in function of the bladder throughout the history of the hernia.

[COMPILERS' NOTE.—Perineal hernias of the bladder are extremely rare. They are more commonly observed among females than among

males. The condition must be distinguished from rectocele, cystocele and other ectopic conditions of the lower part of the urinary tract. In a review of 15 cases of diverticulum of the urinary bladder associated with hernia, tabulated by Lowsley and Gutierrez,[51] not a single instance of this perineal type of hernia is mentioned. It is obvious that it is most important to establish a correct diagnosis of this acquired or congenital lesion previous to its surgical repair; accurate diagnosis can be aided by the routine use of cystography.]

Function.—Smith and Engel [52] came to the conclusion that the normal motor function of the bladder is maintained by balanced innervation from the sympathetic and the parasympathetic nerves. The parasympathetic nerves are capable of carrying on vesical function independently, and the action of the sympathetic nerves on the sphincteric outlet is brakelike, relatively speaking, a retarding balance against the action of the parasympathetic nerves.

Retention or incontinence must be considered in the following respects: first, as to whether retention is the result of anatomic obstruction, or defective innervation, which must be determined by cystoscopy and cystography; second, as to whether incontinence is the result of overflow of retained urine or a complete absence of sphincteric control; third, as to which division or part of the autonomic nerve supply is affected. Smith and Engel stated that personal experience and a survey of current literature indicated that in most instances responsibility for either incontinence or retention can be placed on faulty innervation from the parasympathetic nerves, which in most instances is associated with osseous fusional defects of the lower part of the spinal column, in which the nerve roots have become involved in associated fibrous tissue during the development of the patient. In cases of retention, degeneration of the parasympathetic nerves apparently leaves the brakelike innervation from the sympathetic nerves in control of the sphincters. Smith and Engel stated that in cases of incontinence the inherent tonus of the sphincter muscles, which is dependent on parasympathetic innervation, was absent from the first in the more aggravated cases, and had been completely lost during the degenerative process, in which primary retention had passed over into incontinence.

Smith and Engel stated that treatment is regarded as essentially surgical. Correction of impingement on nerves involved in osseous spinal defects should receive primary consideration. In cases of incontinence, reenforcement of sphincteric control should be attempted by

51. Lowsley, O. S., and Gutierrez, Robert: Operative Intervention for Relief of Diverticulum of the Urinary Bladder, Analysis of Fifty-Four Cases, J. Urol. **19**:459 (April) 1928.

52. Smith, C. K., and Engel, L. P.: Neurogenic Vesical Dysfunction in Children, J. Urol. **28**:675 (Dec.) 1932.

transplantation of muscles into the perineum, encircling the urethra, or by plastic tightening of the vesical sphincteric outlet. If a sense of filling or emptying of the bladder remains, fair to good results can be expected. On the contrary, if no such sense remains this plan is useless. In cases of retention, resection of the sympathetic chain releases the brakelike action on the sphincter, and good emptying power can be expected.

Cumming [53] stated that observations made on the urinary tract by means of serial roentgenograms, together with the usual functional studies and, in some instances, cystoscopic procedures carried out primarily for treatment, indicate that emptying of the bladder can be established following retention due to injury of the spinal cord or to pressure, as from a tumor, without the use of catheters. In stubborn cases automatic emptying can be facilitated by the use of caudal anesthesia. In case of infection of the bladder, ascending involvement of the kidneys and ureters is universal, and a large proportion of patients who survive the early effects of a lesion of the spinal cord succumb to renal infection. In some instances there seems to be more or less spontaneous recovery from renal infection, but recurrences are frequent. In the presence of gross infection of the urinary tract, with a paralyzed bladder, a great deal can be accomplished toward overcoming or curing this infection by means of routine, accepted types of treatment. Prolonged drainage by a ureteral catheter is particularly efficient. Cumming stated that hydronephrosis is not a common sequel of paralysis of the bladder, nor is ureteral atony a common finding except in the presence of gross infection.

Learmonth and Braasch [54] considered the value of sympathetic neurectomy in vesical conditions. They drew attention to what seemed to them to be a significant fact, as far as their material allowed them to judge. Cases are found in each of the three groups in which section of the presacral nerve alone was effective, either as a primary operation or after local procedures had failed. They expressed the opinion, therefore, that in suitable cases the possibility of using this procedure should be considered. As time passes, no doubt the indications for the operation will be more strictly defined, and this may mean either restriction of its field or expansion to include other conditions. The authors expressed themselves as being satisfied that the procedure had occasional value in their own practice.

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53. Cumming, R. E.: Structural and Functional Changes in Urinary Tract Following Focal Cord Lesions, J. A. M. A. **99**:1998 (Dec. 10) 1932.

54. Learmonth, J. R., and Braasch, W. F.: Clinical and Surgical Aspects of Nerve Lesions Involving the Lower Part of the Urinary Tract, Ztschr. f. urol. Chir. **36**:195 (Jan.) 1933.

TESTIS

Tumor.—Zondek [55] has studied the behavior of the anterior hypophyseal hormone in 14 cases of teratoma of the testis; the ages of the patients varied from 30 to 66 years. He pointed out that the excretion of prolan A by patients with tumors is usually somewhere between a physiologic minimum and the greatly increased excretion found in pregnancy. (Embryonal adenocarcinoma and chorionepithelioma of the testis result in the excretion of from two to five times the amount of anterior hypophyseal hormone found in pregnancy.)

Control tests were made on the urine of healthy men and on that of men with various types of internal disease. In all, the reaction was negative. In view of this, Zondek concluded that in men a positive reaction may be interpreted as evidence of a malignant tumor of the testis.

Zondek stated that it may be possible to demonstrate a definite relationship between the excretion of prolan A in the urine and the type of testicular tumor; he points out the wide variation in the amount excreted in cases of chorionepithelioma and of teratoma. He closed his study with a plea that the urine of patients suffering from testicular tumors be regularly examined for the hormone of the anterior hypophysis.

Bollag [56] stated that malignant tumors of the testis occur most frequently between the ages of 25 and 35 years. The most frequently observed etiologic factors are ectopia of the testis and trauma. Earlier therapeutic methods consisted chiefly in simple castration or radical operation, including removal of the pelvic and abdominal lymph nodes. Since 1923 more patients are being treated by extirpation of the primary tumor with postoperative irradiation. The author found in the literature reports of 47 cases in which results were satisfactory.

Although the last ten years have shown progress in studies of the etiology and treatment of testicular tumors, there is still an important field for investigation of these tumors from the point of view of hormones. In this connection, Zondek has urged study of the anterior hypophyseal hormone. In several cases, chiefly cases of chorionepithelioma of the testis, but including also 5 cases of testicular sarcoma, the hormone was demonstrated. The demonstration can be made by injection of the urine or extracts therefrom (after the technic of Zondek), or by the implantation of fragments of tumor into immature female mice.

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55. Zondek, Bernhard: Maligne Hodentumoren und Hypophysen Vorderlappenhormone, Klin. Wchnschr. **11**:274 (Feb.) 1932.

56. Bollag, Louis: Zur Kasuistik der malignen Hodentumoren, Schweiz. med. Wchnschr. **62**:419 (April) 1932.

The author reported 2 cases of seminoma in which the hormone of the anterior lobe of the hypophysis was demonstrated.

PENIS

Carcinoma.—Leighton [57] made a summary of 67 cases of carcinoma of the penis. Of the 24 patients who refused treatment, 1 died of carcinoma and 1 of an unknown cause; 19 had not been heard from, and 1 was operated on elsewhere. Of 43 patients treated conservatively, 4 received roentgen or radium therapy. Three of these died and 1 was not traced. Of 34 cases in which operation was performed, partial amputation was done in 3 cases, and partial amputation with inguinal dissection in 5 cases. Total amputation was done in 1 case.

Of 11 patients who were subjected to total amputation with inguinal dissection, 3 died. Total emasculation was done in 14 cases; 2 of the patients could not be traced, and 9 of the remainder died.

Five of the 34 patients operated on had not been heard from; 14 died, 2 postoperatively and 3 of recurrence; 9 lived from one month to eighteen years, and died of other causes than carcinoma. Nineteen patients were living for from six months to twenty-five years after operation. In each of the 3 cases in which death occurred from recurrence, there was metastasis in the inguinal lymph nodes at operation. Five patients whose tumors were of grade 2, and who had inguinal metastasis at the time of operation, were still alive and free from recurrence at the time of the study.

[COMPILERS' NOTE.—Papillary or flat carcinoma of the penis, usually arises beneath a tight, redundant prepuce. The value of the prophylactic procedure of circumcision in youth cannot be too greatly emphasized. Advocates of radical operation, such as the procedure outlined by Young, and of roentgen therapy, vie with one another in reporting excellent end-results. Increasing evidence shows the superiority of radium treatment if applied early and before invasion of Buck's fascia. Here again the prognostic importance of the grade of malignancy in determining the probability of cure, or of the length of life after any form of treatment, is noteworthy.]

UROGRAPHY

Wesson and Fulmer [58] stated that pyelography after intravenous injection should be used in any case in which the presence of stone in the ureter is suspected. If the medium is eliminated equally well from

57. Leighton, W. E.: Carcinoma of the Penis, with a Report of Sixty-Seven Cases, Am. J. Cancer **16**:251 (March) 1932.

58. Wesson, M. B., and Fulmer, C. C.: Influence of Ureteral Stones on Intravenous Urograms, Am. J. Roentgenol. **28**:27 (July) 1932.

both kidneys, no stone is present. This type of pyelography is not of direct value in the diagnosis of obstructing ureteral stones which do not cast shadows, but is of distinct value in excluding stones from the diagnosis. In cases of acute ureteral stone, the pyelogram on the unaffected side will be good, and on the affected side, evidence of increased density of the kidney but no outline of the pelvis or ureter, or a very much delayed one, will be seen.

The authors stated that in the presence of ureteral stones that partially block the ureter and cause stasis and hydronephrosis, the pelvis is usually well outlined. If the stone blocked the ureter completely, there would be a functionless kidney above, and hence no pelvic shadow. The early reflex inhibition from ureteral irritation acts to protect the kidney from early hydronephrosis. The reduction in ability to secrete the medium is apparent rather than real. The increased density of the affected kidney indicates that there is a concentration of the medium between the glomeruli and the distal end of the connecting tubules, the medium being of equal concentration in the blood of both kidneys.

URINARY INFECTION

Campbell,[59] after reviewing 274 of his own cases of chronic pyuria in juvenile patients, stated that under the diagnosis of chronic pyelitis or chronic cystitis, infants and children are commonly and unsuccessfully treated for months or years. When renal infection exists, the lesion is basically suppurative pyelonephritis. In many cases of so-called pyelitis, the infection is localized in the bladder and urethra. When chronic urinary infection resists intensive medical treatment for one month, a complete urologic examination is indicated. Campbell has found, in infants and children, almost every lesion of the urinary tract which one is accustomed to associate with adult life. As a rule, medical treatment alone is inadequate to effect bacteriologic cure, and while surgical attack may serve only to control rather than to cure the infection, conservative operations often will prevent further renal destruction and thus prove life-saving. Occasionally, nephrectomy is demanded.

May[60] stated that infestation with Trichomonas, which is rather common in the vagina, is only rarely found in the urinary tract. He cited the case of a man, aged 51, who had a pain in the right renal region. He had no urinary disturbances, urethral discharge or hematuria. Physical examination gave essentially negative results. Following thorough irrigation of the urethra and bladder, the prostatic

59. Campbell, M. F.: Chronic Urinary Infection in Infancy and Childhood, J. A. M. A. **99**:2231 (Dec. 31) 1932.

60. May, Ferdinand: Trichomonas vaginalis-Infection der Harnwege, Ztschr. f. urol. Chir. **35**:213, 1932.

secretion contained pus cells and Trichomonas vaginalis. There were a few leukocytes and Trichomonas vaginalis in the urine.

The author was unable to find in the literature a report of a similar case affecting a male and only a few in which the urinary tract of a woman was infested with Trichomonas.

URINARY ANTISEPSIS

Davis and Sharpe [61] stated that hexylresorcinol (dose, 0.75 Gm.) exerts an irregular and transient antiseptic action in about one third of the four hour samples. Methenamine (dose, 1 Gm.) is comparatively more efficient than either pyridium or hexylresorcinol in causing the normal person to secrete urine which is antiseptic against both the colon bacillus and the staphylococcus. Acriflavine (dose, 0.2 Gm.), administered in capsules, exerts a surprisingly uniform and consistent antiseptic action in normal urine against both the colon bacillus and the staphylococcus. Urinary alkalinity is essential. On the other hand, acriflavine (dose, 0.2 Gm.), administered in shellac-coated pills, is practically inert. The acriflavine administered in capsules, although not injurious in efficient doses, causes unpleasant symptoms (nausea and catharsis) in a fairly large proportion of cases. Consequently, acriflavine has its definite clinical limitations. Clinical experience indicates, however, that this drug is of distinct value in selected cases, particularly those of acute infection of the urinary tract.

Davis and Sharpe concluded that, as determined by antiseptic tests of samples of urine obtained before and after administration in unit maximal dosage to normal persons, pyridium is practically inert, hexylresorcinol is slightly antiseptic, methenamine is efficient and acriflavine (in alkaline urine) is unfailing.

Davis and Sharpe stated that in the treatment of infections of the urinary tract, the time has not yet arrived when the old reliable methods, based on detailed investigation and elimination of the accessory or underlying causes, may be discarded in favor of indiscriminate medication.

UROLOGIC BACKACHE

Morris, Langlois and Brunton,[62] in a review of 3,600 histories, found backache of urologic origin in 1,127 cases (31 per cent). In this group there were 620 female and 507 male patients. The majority of patients with chronic renal lesions refer to their disability as backache and not as pain in the back. The backache of pyelitis is a constant,

61. Davis, Edwin, and Sharpe, J. C.: Urinary Antisepsis, J. A. M. A. **99**:2097 (Dec. 17) 1932.

62. Morris, H. L.; Langlois, L. J., and Brunton, J. F.: Urologic Backache, J. A. M. A. **99**:2237 (Dec. 31) 1932.

dull, deep-seated ache, diffusely felt in the lumbodorsal region. The backache of ptosis is similar to that of chronic pyelitis, but in addition is of a dragging character and is relieved by rest. The disability in renal calculous disease is not true backache, but a persistent, paroxysmal pain in the costovertebral region, which is intensified and radiates as the calculus passes through the ureter. Prostatic backache is a dull, aching, sacral disability, which is most severe on rising and is occasionally referred along the course of the sciatic nerve.